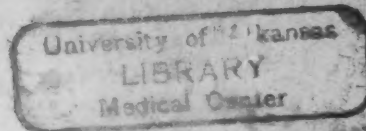


February, 1960  
volume 79, number 2



**COPY 2**

*American  
Journal*  
**of OBSTETRICS  
AND GYNECOLOGY**

*Editor in Chief*

HOWARD C. TAYLOR, JR.

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*Official Publication*

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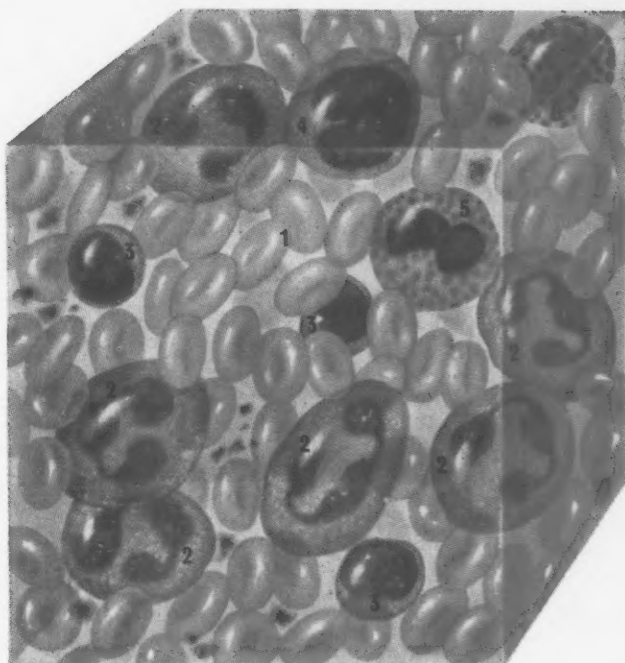
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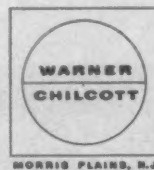
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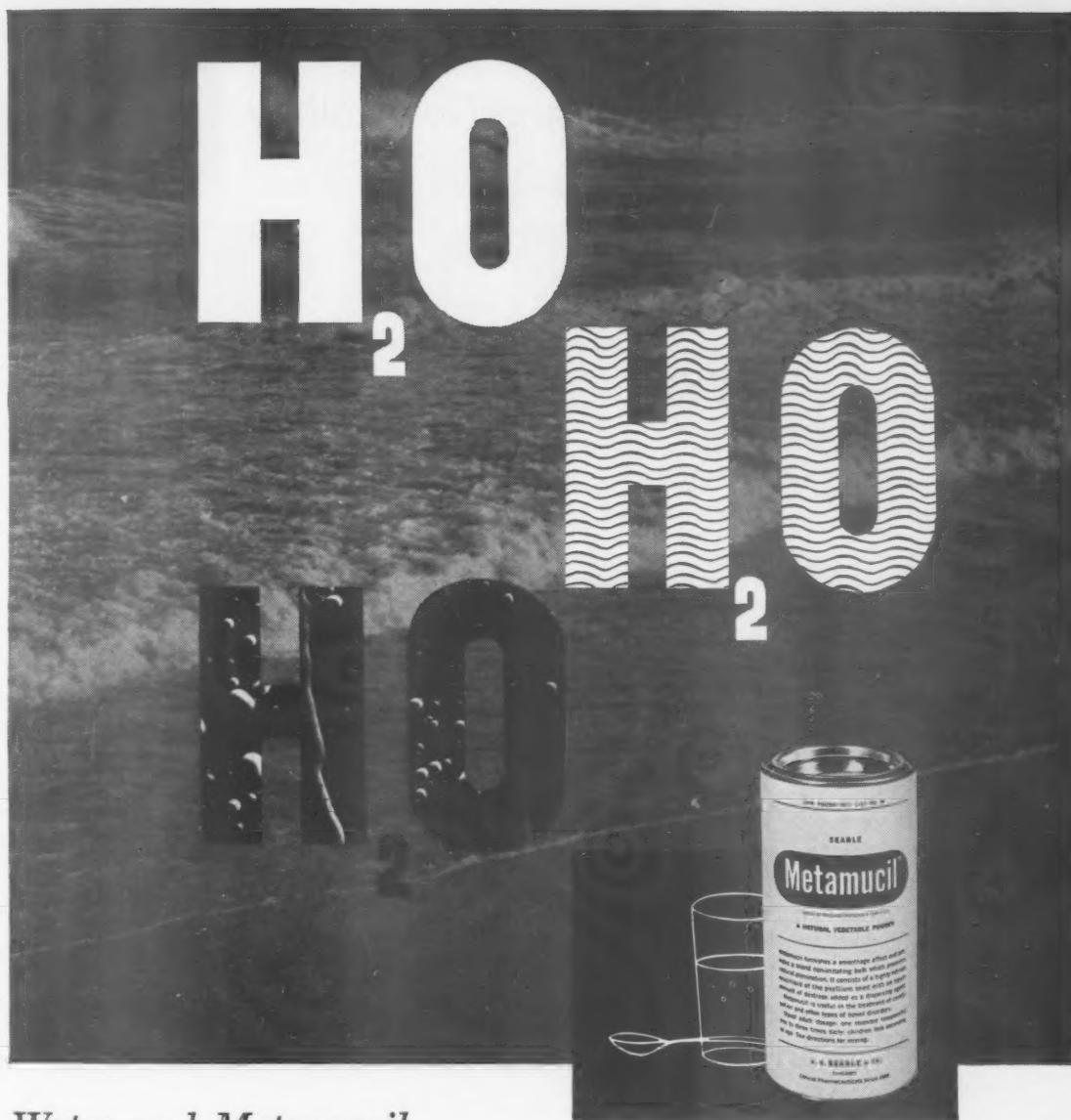
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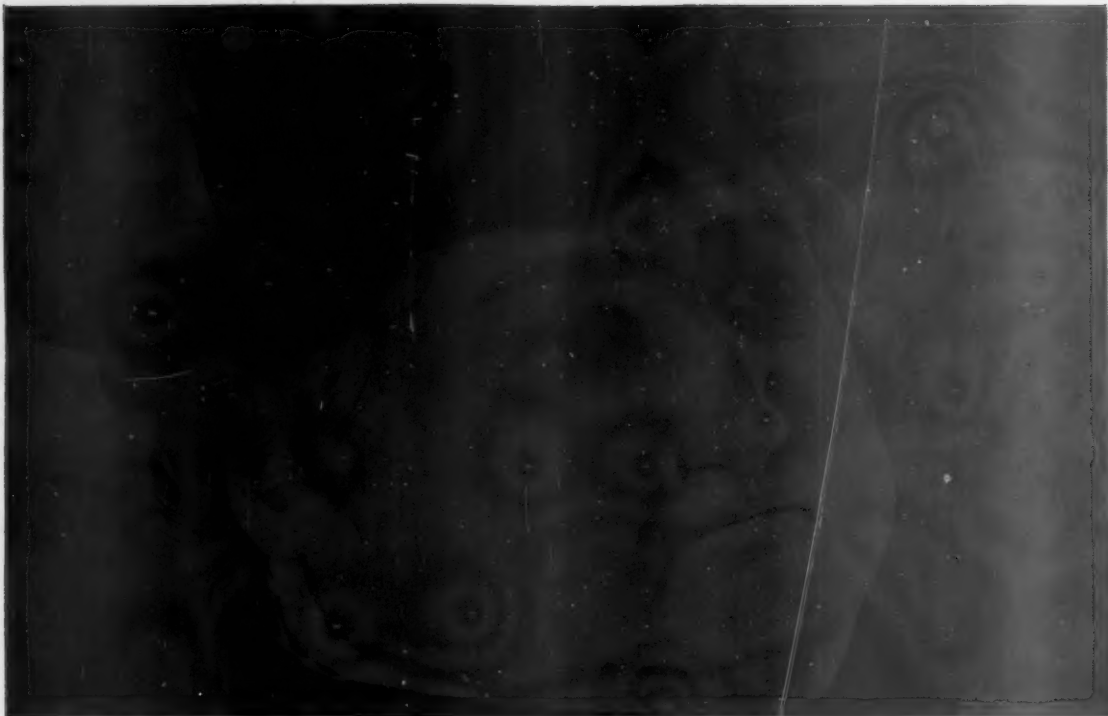
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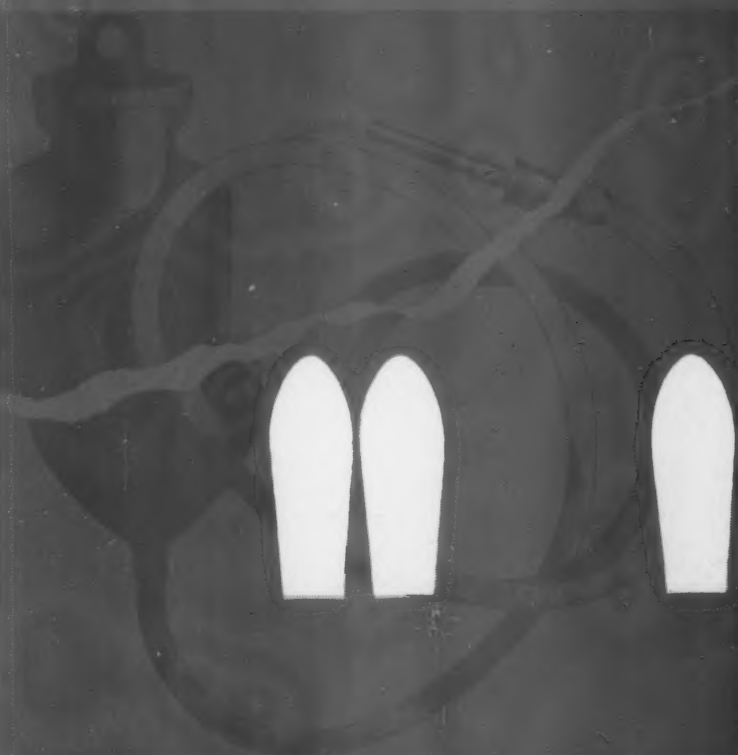


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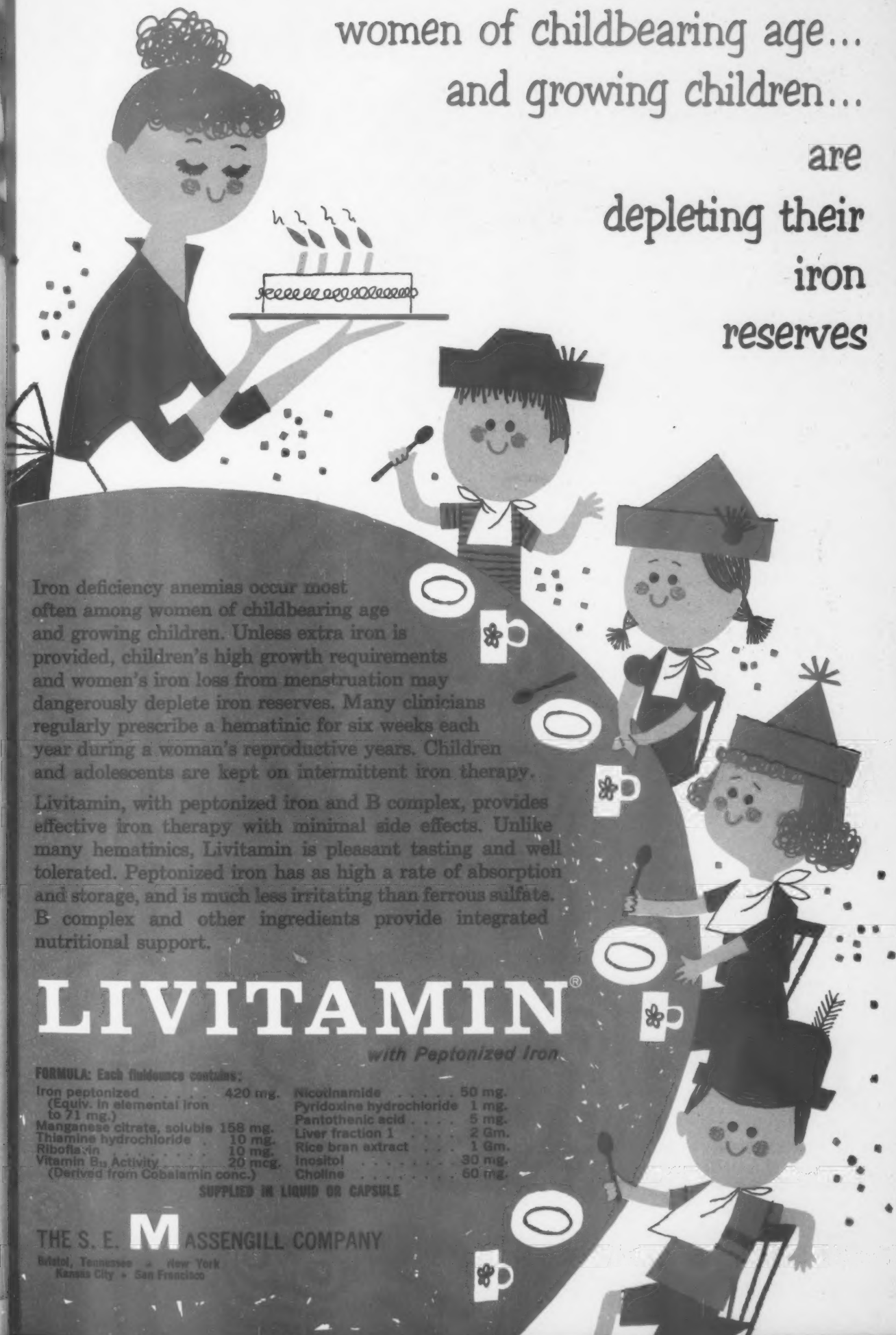
**FORMULA:** Each fluidounce contains:

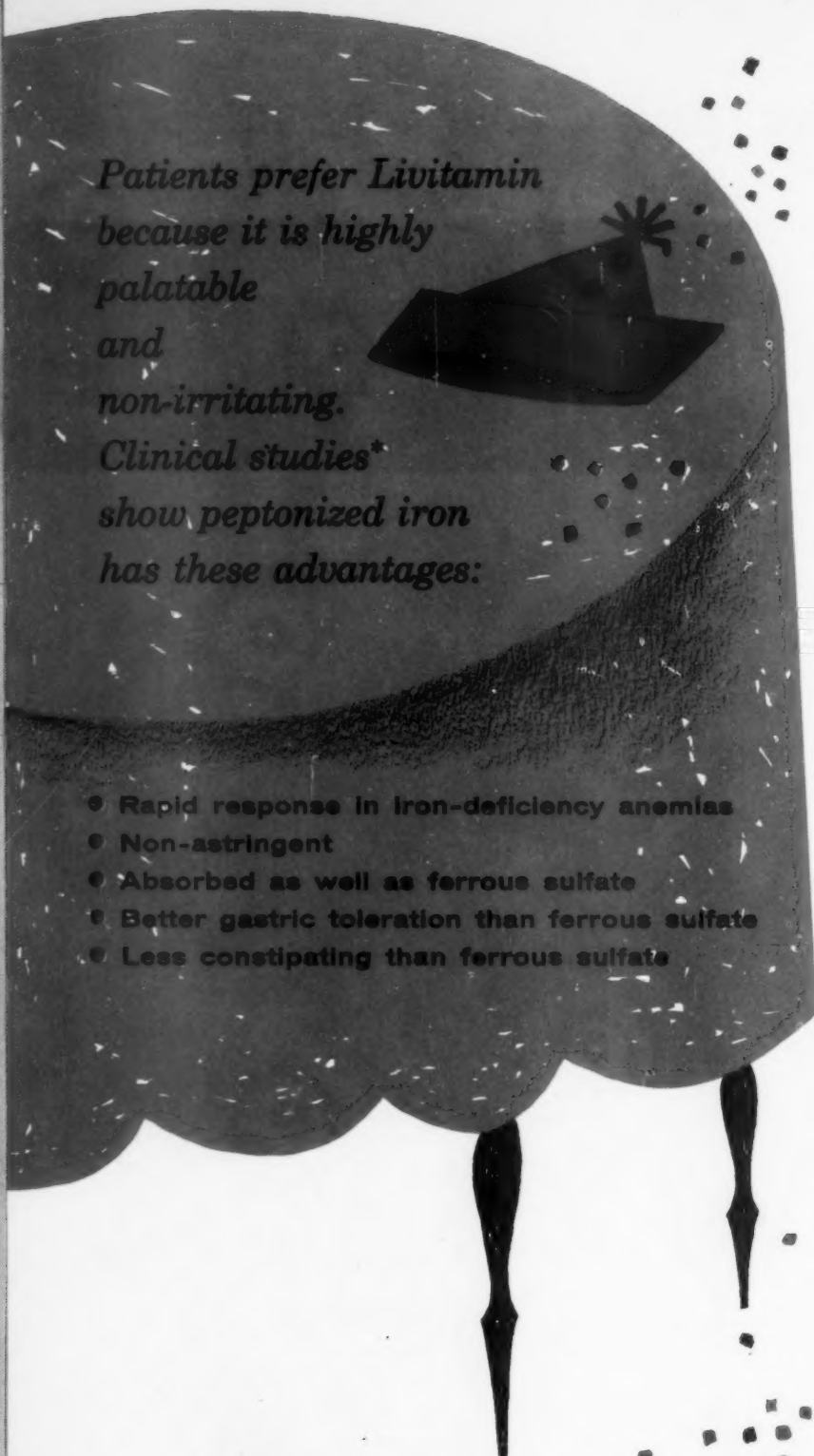
Iron peptonized	420 mg.	Nicotinamide	50 mg.
(Equiv. in elemental iron to 71 mg.)		Pyridoxine hydrochloride	1 mg.
Manganese citrate, soluble	158 mg.	Pantothenic acid	5 mg.
Thiamine hydrochloride	10 mg.	Liver fraction 1	2 Gm.
Riboflavin	10 mg.	Rice bran extract	1 Gm.
Vitamin B <sub>12</sub> Activity	20 mcg.	Inositol	30 mg.
(Derived from Cobalamin conc.)		Choline	60 mg.

SUPPLIED IN LIQUID OR CAPSULE

THE S. E. **M**ASSENGILL COMPANY

Bristol, Tennessee • New York  
Kansas City • San Francisco





*Patients prefer Livitamin  
because it is highly  
palatable  
and  
non-irritating.*

*Clinical studies\*  
show peptonized iron  
has these advantages:*

- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate

# LIVITAMIN<sup>®</sup> *with Peptonized Iron*

... the preferred  
hematinic

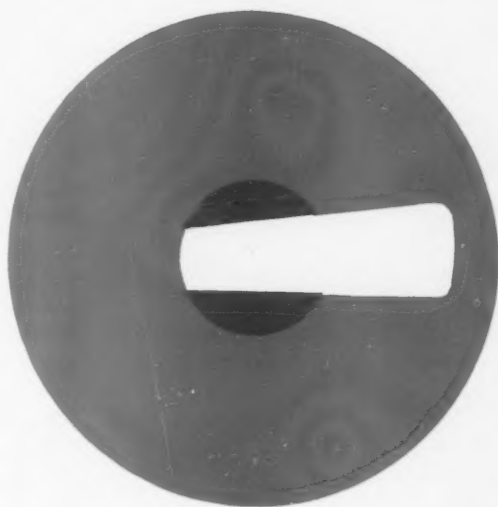
\*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

THE S. E. **M**ASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco

enhanced utility  
for special needs

# NEW FURACIN<sup>®</sup> brand of nitrofurazone INSERTS

(FORMERLY FURACIN URETHRAL SUPPOSITORIES)



0.2% Furacin and 2% dipherodon • HCl,  
an efficient local anesthetic, in a water-  
dispersible base. Each hermetically  
sealed in silver foil, box of 12.

---

"extremely convenient and effective" ...  
"for topical treatment of infections in  
relatively inaccessible body orifices or  
wound sinuses"

Gilliotte, B. W.: Clin. Med. 6:223, 1959

**NOW PRESCRIBED FOR** ■ *draining wound sinuses (surgical or traumatic)*  
■ *juvenile vulvovaginitis* ■ *infections of the nares, external auditory*  
*canal, endocervix and anorectum* ■ *as well as for urethral indications*

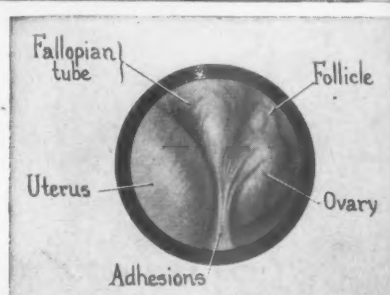
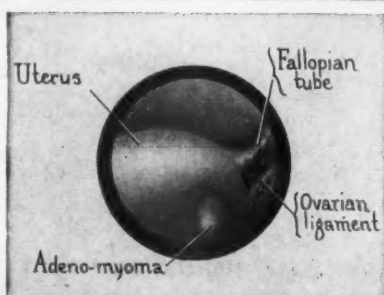
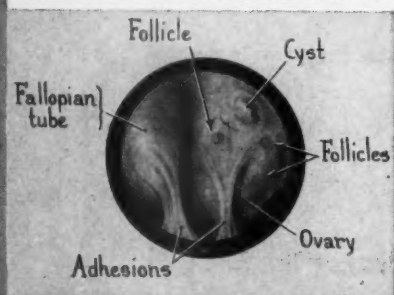
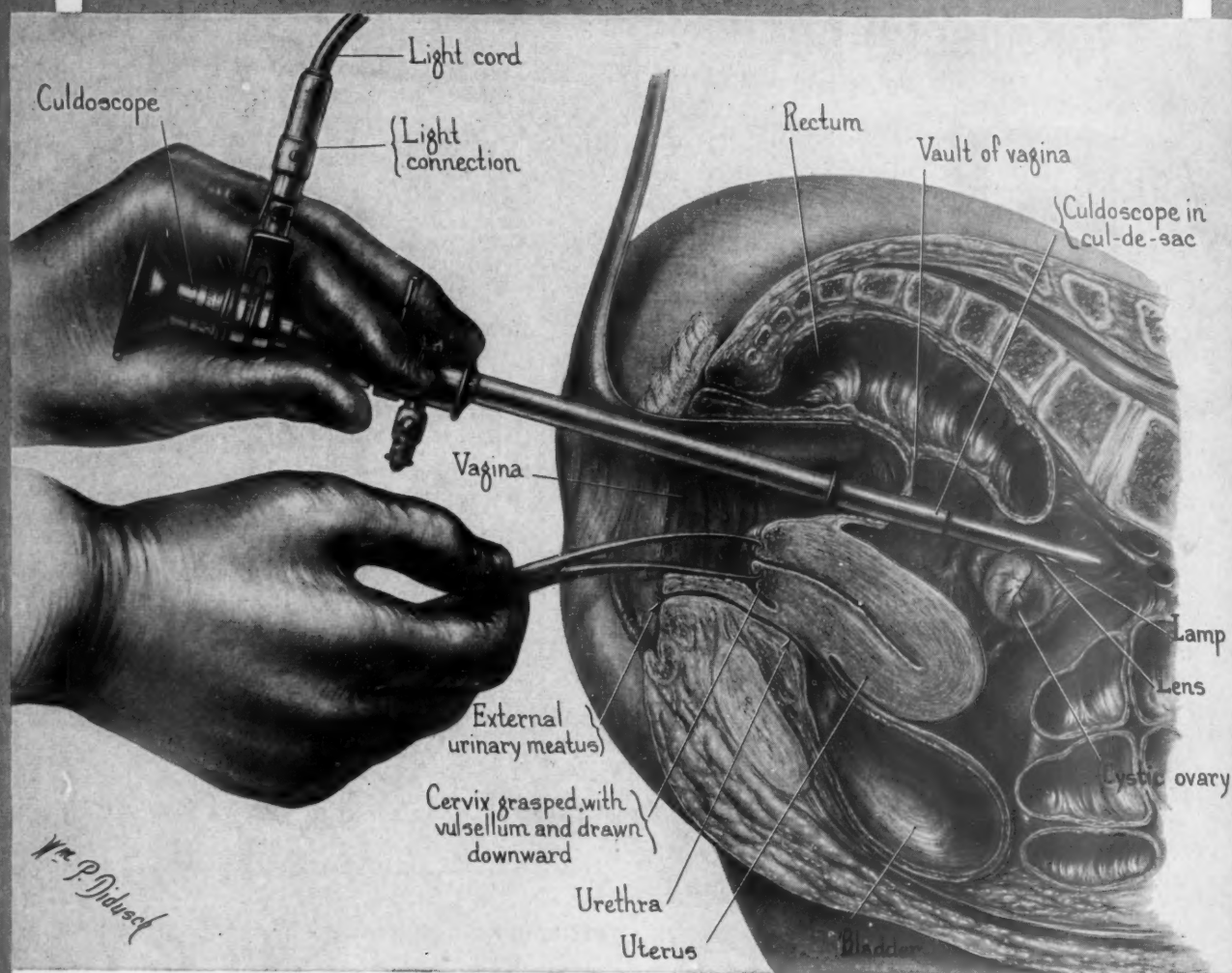
■ provide adequate antibacterial concentrations at hard-to-reach sites of  
infection ■ relieve local pain and discomfort ■ slender, tapered shape  
permits easy introduction

NITROFURANS...a unique class of antimicrobials  
EATON LABORATORIES, NORWICH, NEW YORK



*The Decker*

# CULDOSCOPE



The illustration above shows the Decker Culdoscope in endoscopic visualization of the female pelvic structures by the vaginal route. It permits direct study of pelvic tumors, ovarian pathologies, ectopic pregnancy, endometriosis, pelvic and intestinal adhesions, etc.

ESTABLISHED IN 1900



BY REINHOLD WAPPLER

FREDERICK J. WALLACE, President

*American Cystoscope Makers, Inc.*

8 PELHAM PARKWAY

PELHAM MANOR, N. Y.

IN HEARTBURN OF PREGNANCY, PATIENTS SAY...  
TASTY IS THE WORD FOR

# titralac<sup>®</sup>

TABLETS  
and  
"teaspoon dose"  
LIQUID

UNIQUE ANTACID WITH MILK-LIKE ACTION

TITRALAC is being widely prescribed in heartburn of pregnancy, simple hyperacidity, and peptic ulcer because of these outstanding features:

- creamy, mint flavor... no chalky taste
- acts in seconds... lasts for hours
- non-constipating... no acid rebound

TITRALAC is effective in small doses. One teaspoonful TITRALAC Liquid approximates 2 tablets which contain 0.36 Gm. glycine and 0.84 Gm. calcium carbonate.

ACID NEUTRALIZING POWER

only 1 teaspoonful

or  
2 tablets



ALSO WITH A SPASMOLYTIC...

**titralac-sp**  
(Titralac formula + 0.5 mg. homatropine methylbromide)



*Schenlabs*

SCHENLABS PHARMACEUTICALS, INC.  
NEW YORK 1, N. Y.

Manufacturers of NEUTRAPEN<sup>®</sup>  
for penicillin reactions

© T.M. REG. U.S. PAT. OFF.



New! ...for appetite control



## Helps you keep your patient on your diet

**DOES MORE THAN CURB APPETITE ...  
ALSO RELIEVES TENSIONS OF DIETING**

**AN EXTENSIVE SURVEY** shows that in 68% of overweight persons there is an emotional basis for failure to limit food intake.<sup>1</sup> Appetrol has been formulated to help you overcome this problem and to keep your overweight patient on your diet.

**THIS NEW ANORECTIC** does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.

**IN PRESCRIBING APPETROL**, you will find that your patient is relaxed and more easily managed so that she will stay on the diet you prescribe.

**Usual dosage:** 1 or 2 tablets one-half to 1 hour before meals.

**Each tablet contains:** 5 mg. dextro-amphetamine sulfate and 400 mg. Miltown (meprobamate, Wallace).

**Available:** Bottles of 50 pink, scored tablets.

1. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.

# Appetrol®

DEXTRO-AMPHETAMINE + MILTOWN®

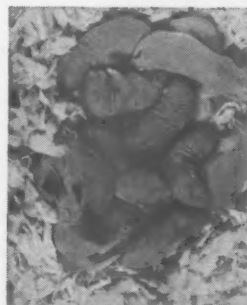


WALLACE LABORATORIES / New Brunswick, N. J.

**Upjohn**

announces  
the first progestin  
since progesterone  
that will maintain pregnancy  
even in ovariectomized rats

Ovariectomy of the rat in early pregnancy invariably leads to abortion unless progestin is substituted. Here, rat was ovariectomized on 9th day, and pregnancy maintained on medroxyprogesterone until 21st day, when pups were taken by cesarean section. (From a scientific exhibit, AMA annual meeting, June, 1959).



For the  
promise of  
this new  
compound in your  
practice,  
please turn  
page

## The most welcome pain in the world

How much better a pain in the uterus than an ache in the heart! It is pure ecstasy to the habitual aborter, to whom it signifies the imminent fulfillment of her fondest dream.

Only you who have shared her anguish through repeated abortions can fully appreciate her soaring sense of achievement at having finally reached term. Knowing, as you do, the maddening frustration of being powerless to prevent her previous abortions with the ineffective measures that were available at that time, your sense of achievement now parallels hers.

This is the promise of Provera—a new, oral progestin developed by Upjohn research. Because it represents the first clinically-significant improvement on progesterone, we believe Provera constitutes the most important advance in the treatment of idiopathic recurrent abortion in 30 years.

It is the only compound, other than pro-

gesterone, that will maintain pregnancy in ovariectomized rats. And it is approximately 40 times as potent as progesterone, which makes oral therapy of habitual abortion practical for the first time.

And Provera exerts no significant androgenic or estrogenic effect whatever—which makes it a “purer” progestational agent than progesterone itself.

We invite you to select the most critical 60 days of pregnancy as your test. Use Provera (10 to 20 mg./day) to carry your next habitual aborter through the dangerous period during which the production of endogenous progesterone shifts from the corpus luteum to the placenta (usually in the third and fourth months). The cost to your patient will be a pleasant surprise.

For full details, ask your Upjohn representative, or write Department of Product Information, Medical Division, The Upjohn Company, Kalamazoo, Michigan.



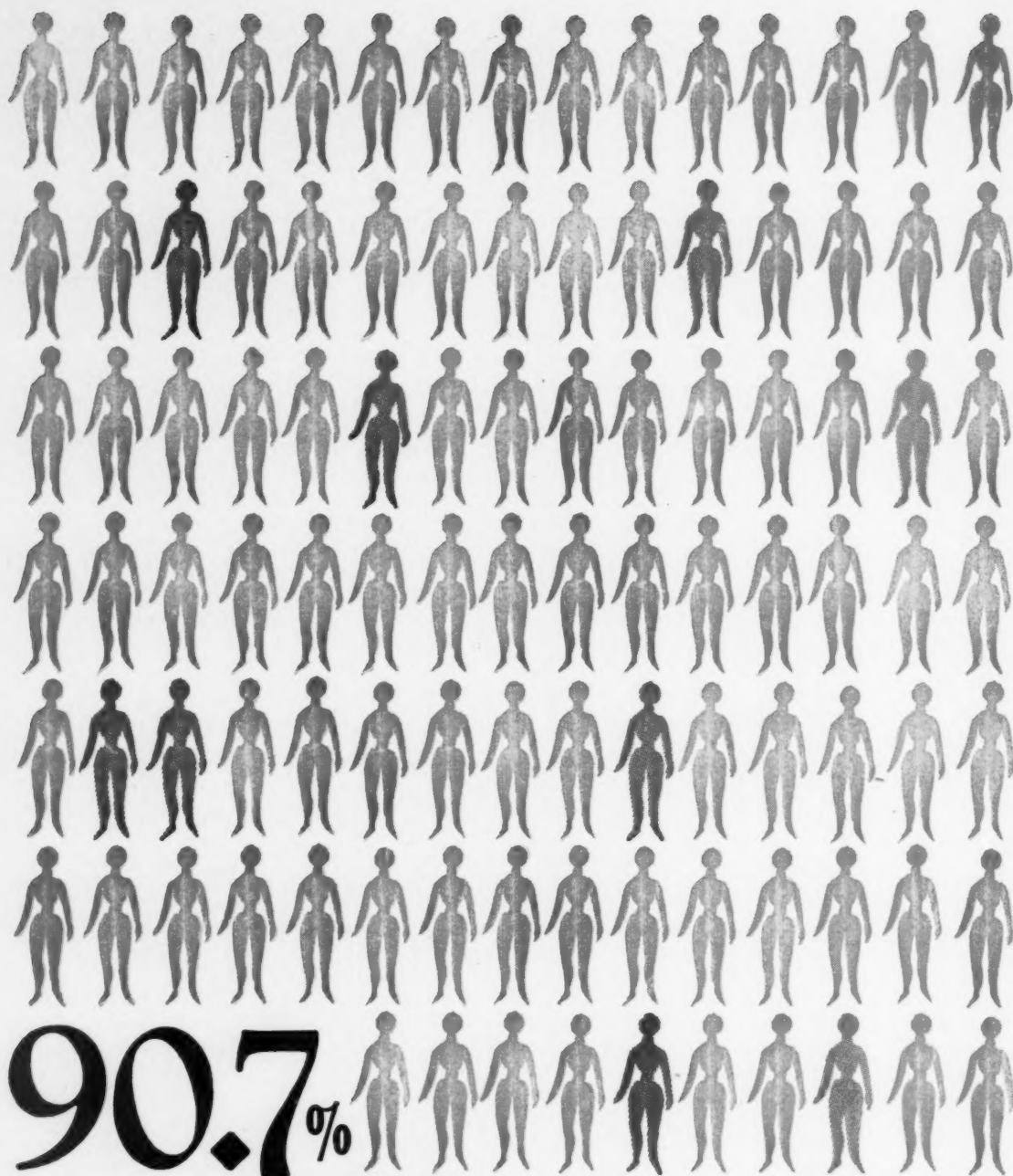


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# PROVERA\*

**Upjohn**

\*Trademark, Reg. U.S. Pat. Off.  
Medroxyprogesterone acetate, Upjohn



**90.7%**  
**successful pregnancies**

With the addition of Nugestoral to their anti-abortive regimen, Murphy *et al.*\* brought 78 of 86 habitual aborters to full-term. Nugestoral helps by providing in each daily dose of three tablets 45.0 mg. Progestoral® (ethisterone), 525.0 mg. vitamin C, 487.5 mg. purified hesperidin, 6.0 mg. vitamin K, 10.5 mg. vitamin E. Boxes of 30 and 100.

**NUGESTORAL®**



Organon Inc.  
 Orange, New Jersey

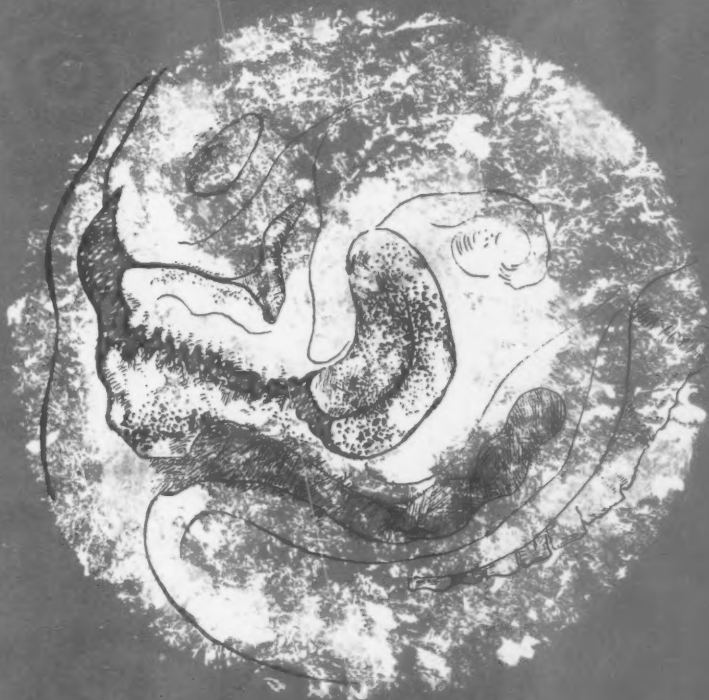
\*Murphy, H. S., et al., Scientific Exhibit, A.M.A., Dec. 1-4, 1959, Dallas, Texas.



*the true specific  
for  
monilial vaginitis*

# GENTIA-JEL<sup>®</sup>

*CURES ARE QUICKER* Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. *IMMEDIATE RELIEF* This soothing jel provides fast, gratifying relief of vulvar itching and burning . . . destroys fungi and bacteria. *COMPLETE COVERAGE* Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.



*start therapy  
with GENTIA-JEL  
. . . it works  
when others fail*

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York

# GENTIA-JEL

*the true specific  
for monilial vaginitis*

Gentian violet is the most effective agent known for the destruction of *Monilia albicans*. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monilial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never re-used, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.



**WHY WAIT UNTIL OTHER THERAPIES FAIL...  
START YOUR PATIENTS WITH GENTIA-JEL**

**WESTWOOD PHARMACEUTICALS**

**Buffalo 13, New York**



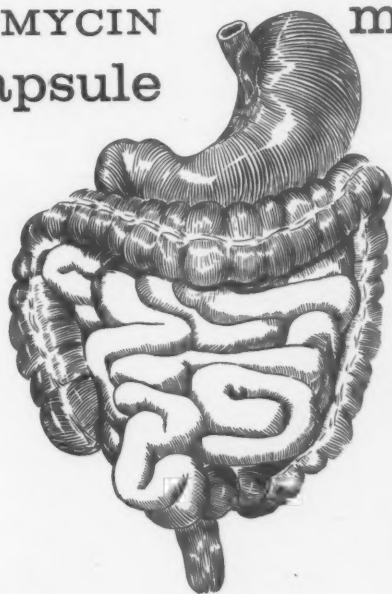




# DECLOMYCIN NOTES:

Demethylchlortetracycline Lederle

antibiotic  
**toleration**  
reduction in incidence and/or severity of gastrointestinal side effects may be attributed to the far lower  
**DECLOMYCIN** milligram intake  
(per capsule and per day)<sup>(1-3)</sup>



1. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline. Presented at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959. 2. Hirsch, H. A.; Kunin, C. M., and Finland, M.: Demethylchlortetracycline—A New and More Stable Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Activity. München. med. Wchschr. To be published. 3. Lichter, E. A., and Sobel, S.: The Distribution of Oral Demethylchlortetracycline in Healthy Volunteers and in Patients Under Treatment for Various Infections. To be published.

Capsules, 150 mg.—Pediatric Drops, 60 mg./cc.—Oral Suspension, 75 mg./5 cc. tsp.

GREATER ACTIVITY...FAR LESS ANTIBIOTIC...UNRELENTING-PEAK CONTROL..."EXTRA-DAY" PROTECTION AGAINST RELAPSE

 **LEDERLE LABORATORIES**, a Division of **AMERICAN CYANAMID COMPANY**, Pearl River, N.Y.

when surgery or childbirth stops intestinal peristalsis

Ure

stalsi

# Urecholine

Chloride

(Bethanechol Chloride)

helps restore normal gastrointestinal function  
—without uncomfortable enemas or intubation

Because it stimulates peristalsis, URECHOLINE helps restore normal gastrointestinal function. Given prophylactically soon after surgery or childbirth, or therapeutically when abdominal distention occurs, URECHOLINE facilitates expulsion of gas and promotes evacuation. *Supplied:* 5 mg. and 10 mg. tablets, bottles of 100. 1-cc. ampuls containing 5 mg.


For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

URECHOLINE IS A TRADEMARK OF MERCK & CO., INC.

**in cardiac edema of  
varying severity**



**weight loss ranged  
from 4 to 45 lbs. on**

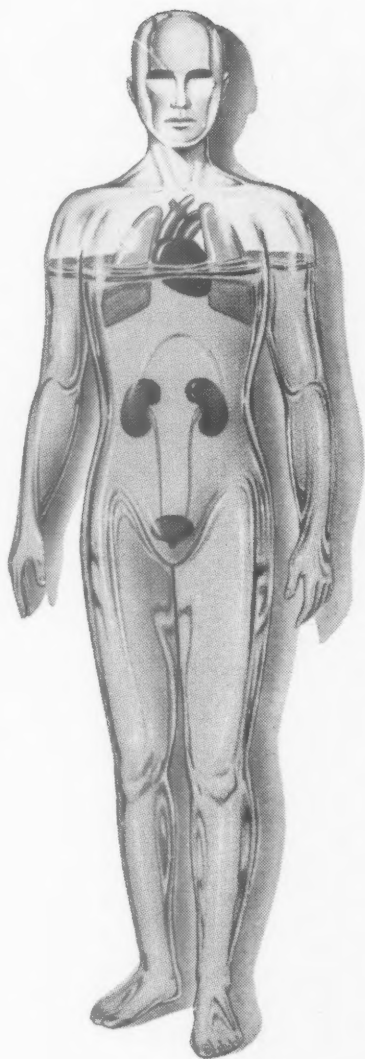
**HYDRODIURIL<sup>®</sup>**

HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects



*Sackner, M. A., Wallack, A. A. and Bellet, S.: Am. J. M. Sc. 237:575, (May) 1959.*



“The severity of the congestive heart failure . . . was as follows: Class IV (9 patients), Class III (5 patients), and Class II (1 patient).” . . . “Weight loss ranged from 4 to 45 pounds over a period of 3 to 17 days with an average of 2.4 pounds a day.”

**DOSAGE:** One or two 50 mg. tablets of HYDRODIURIL once or twice a day.

**SUPPLIED:** 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., Inc.

Additional information on HYDRODIURIL is available to the physician on request.



**MERCK SHARP & DOHME**  
Division of Merck & Co., Inc. Philadelphia 1, Pa.

how  
much  
**IRON**  
is  
needed?



appreciably less with ...

# Fermalox

(Rorer)  
uncoated MAALOX—buffered ferrous sulfate

... and gastric irritation is rare!

**Higher absorption, lower dosage, greater tolerance:** When FERMALOX is prescribed in anemia, "satisfactory clinical response is obtained with 44% of U.S.P. dosage."<sup>1</sup> Uncoated FERMALOX tablets disintegrate rapidly, provide more iron for immediate absorption, increased utilization. The buffering action of MAALOX® virtually eliminates the gastric irritation of iron. For hypochromic anemia the dose is only 2 FERMALOX tablets daily. After 15 days this may be reduced to 1 tablet daily.

Each uncoated FERMALOX tablet contains ferrous sulfate, 200 mg. plus MAALOX-Rorer (magnesium-aluminum hydroxides), 200 mg. Bottles of 100 tablets.

1. Price, A. H., et al.: J.A.M.A. 167:1612, 1958.



**WILLIAM H. RORER, INC.**

Philadelphia 44, Pa.

**Trilafon**<sup>®</sup> perphenazine for the anxiety in  
the person overwhelmed by family  
illness...selective anxiety relief with  
minimal drowsiness or dulling

*Schering*

S-419

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# in rectal inflammation: topical hydrocortisone brings objective improvement

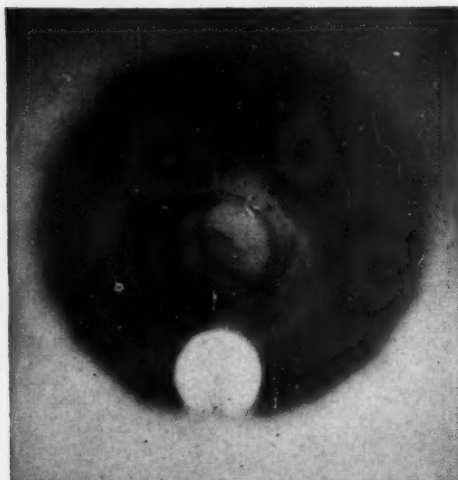
*dramatic decrease in bleeding, discharge, tenesmus ...  
visible mucosal repair*

More than 90 per cent of 37 patients with radiation proctitis showed pronounced improvement when treated topically with hydrocortisone.<sup>1</sup> In nonspecific proctitis with bleeding and ulceration, 1 to 3 weeks of topical hydrocortisone therapy produced marked relief or complete remission.<sup>2</sup>

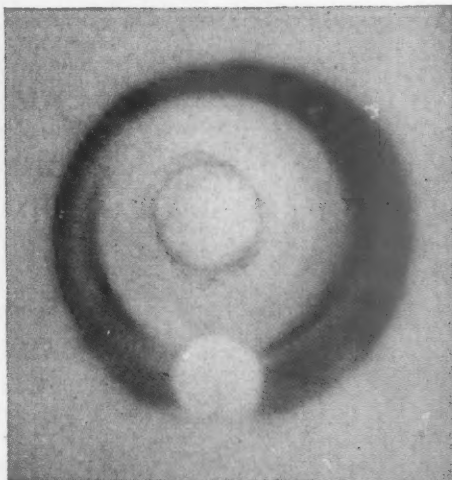
Because rectal absorption of hydrocortisone is minimal,<sup>1</sup> easy-to-use CORT-DOME Suppositories, while exerting potent local anti-inflammatory action, are virtually free of unwanted systemic corticosteroid effects...require no special precautions, except in the presence of rectal infection.

## CORT-DOME<sup>®</sup> 25 mg. Suppositories

high potency hydrocortisone in ACID MANTLE<sup>®</sup> vehicle **DOME** pH 5.4



Ulcerative proctitis in woman, age 38. Rectal bleeding and diarrhea of 2 months' duration.



Same patient after 3 weeks of hydrocortisone suppositories. No further symptoms. Treatment discontinued at this time.

*Indicated* in postirradiation (factitial) proctitis; nonspecific proctitis; chemical and medicinal proctitis; as an adjunct in treatment of chronic ulcerative colitis; cryptitis; other inflammatory conditions of anorectum.

*Available* in boxes of 12. Each foil-wrapped suppository contains 25 mg. hydrocortisone alcohol in a nonirritating ACID MANTLE<sup>®</sup> vehicle.

1. Kaplan, B. J.: Connecticut State M. J. 20:357, 1956. 2. Kaplan, B. J.: Personal communication.



**DOME CHEMICALS INC.** 125 West End Ave., New York 23, N. Y.  
Los Angeles • Montreal





advancing with surgery

ETHICON®



reverse cutting

ATRALOC NEEDLES

20% more strength

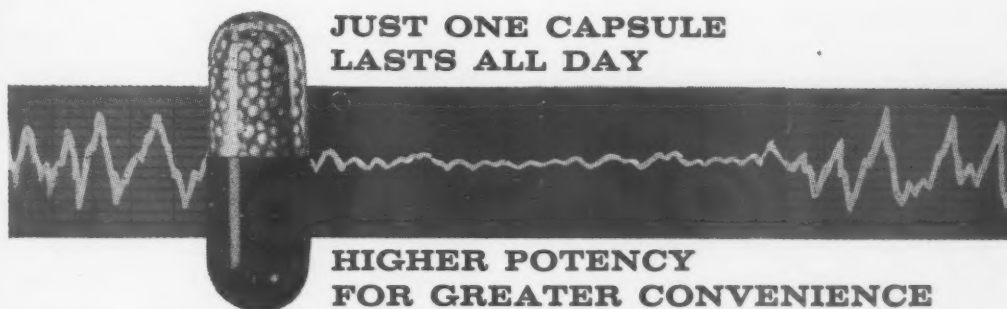
ETHICON®

**NEW AND EXCLUSIVE**

**FOR SUSTAINED  
TRANQUILIZATION**

MILTOWN® (*meprobamate*) now available  
in 400 mg. continuous release capsules as

**Meprospan®-400**



- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

**Usual dosage:** One capsule at breakfast,  
one capsule with evening meal

**Available:** *Meprospan-400*, each blue capsule contains  
400 mg. Miltown (*meprobamate*)  
*Meprospan-200*, each yellow capsule contains  
200 mg. Miltown (*meprobamate*)  
*Both potencies in bottles of 30.*

**W** WALLACE LABORATORIES, *New Brunswick, N. J.*

CHE-8427

**KEEP YOUR  
HYPERTENSIVES  
WIDE AWAKE  
AND WORKING**





# WITH ONE OF THREE PRECISION-TAILORED DOSAGES

# NEW ORETICYL<sup>TM</sup>

(ORETIC<sup>TM</sup> WITH HARMONYL<sup>®</sup>)

**INCLUDING NEW "STARTER" DOSE FORM WITH  
25 MG. ORETIC, 0.25 MG. HARMONYL IN ONE TABLET**

If you want to control your dosage more precisely: Oreticyl is available in three strengths—

**1. Oreticyl Forte**, combining Oretic 25 mg. and Harmony 0.25 mg.

Recommended for initial treatment in many cases of established hypertension of any but minor degree. Oreticyl Forte offers Harmony's full therapeutic effect potentiated by small maintenance dose of Oretic. Usual starting dosage: one tablet t.i.d.

**2. Oreticyl 50**, combining Oretic 50 mg. and Harmony 0.125 mg.

**3. Oreticyl 25**, combining Oretic 25 mg. and Harmony 0.125 mg.

Once the effect of Harmony is seen, usually after 2-3 weeks, dosage may be adjusted by employing either the 25 or 50 strength, depending upon patient response. In some cases of mild hypertension, either Oreticyl 25 or Oreticyl 50 can be used successfully to initiate treatment.

**If you want more convenient therapy:**

This new combination of Oretic and Harmony in a **single tablet** may make it possible to employ a reduced dosage of both agents while still achieving a pronounced antihypertensive effect.

As an antihypertensive, Harmony is equally as effective as rauwolfias in lowering blood pressure, but incidence of side effects—particularly daytime lethargy, nasal stuffiness, depression—is distinctly lower.

**If you want to increase the effectiveness of another agent:** Oreticyl can be safely and effectively combined with other antihypertensives in the treatment of more severe cases.

Ganglionic blocking agents, for example, may be—and should be—administered at just half the usual dose, due to Oreticyl's potentiating effect.

All three Oreticyl strengths are supplied in bottles of 100 and 1000.

**...BRIGHTEN HIS DREARY DIET, TOO**  
Oretic's pronounced saluretic effect often lets you relax rigid low-salt diet restriction, even while Harmony keeps working to bring blood pressure down.

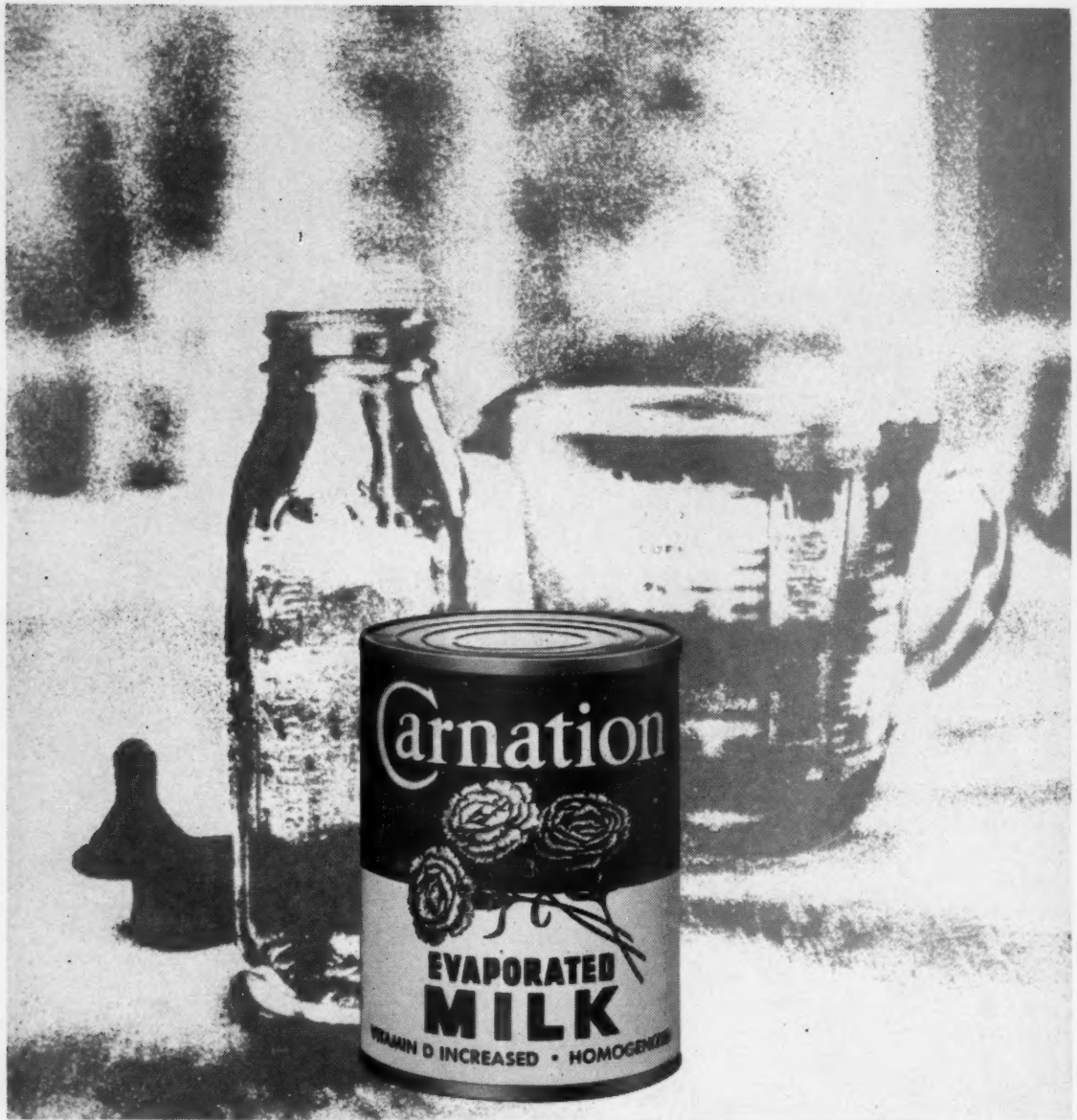


ORETICYL—TRADEMARK FOR ORETIC WITH HARMONYL

ORETIC—TRADEMARK FOR HYDROCHLOROTHIAZIDE, ABBOTT

HARMONYL—DESERPIDINE, ABBOTT

011181



*"from Contented Cows"*

## World's leader by far for infant feeding

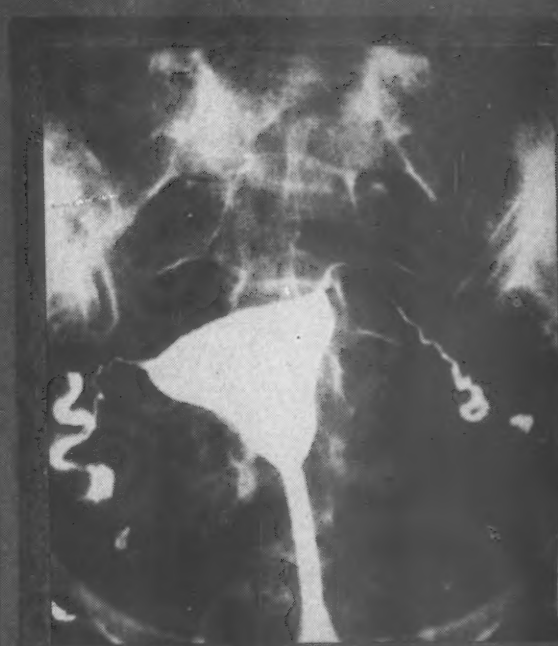
86% of pediatricians prefer the evaporated milk formula. And more babies have been brought up on formulas made with Carnation Evaporated Milk than any other brand.

NOW IN NEW READY-PREPARED FORM, TOO! Carnalac is Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate.\* Mother simply adds water in the amount you recommend, and a balanced formula is assured.



*\*Natural lactose from the milk, and maltose-dextrin syrup*

diagnosis  
without  
delay



**Salpix**<sup>®</sup>  
contrast medium

in hysterosalpingography  
for detecting uterine  
and tubal abnormalities

Ortho Pharmaceutical Corporation  
RARITAN, NEW JERSEY







*"...a much smoother post-natal and postsurgical course...In 91 per cent of all patients, bowel function was manifest four to 48 hours after the initial dose of d-pantothenyl alcohol (COZYME)"\* Due to the increased metabolic rate the maternal body requires additional B vitamins to which pantothenic acid belongs. COZYME supplies the active molecular component of coenzyme A—pantothenic acid—which is essential in the formation of acetylcholine, the chemical mediator of nerve impulse transmission governing intestinal motility.*

Operations and/or Diagnosis	No. of Patients	Hours between first dose of Cozyme and return of bowel activity
<b>Nonsurgical</b>		
Uncomplicated OB delivery	22	4 to 12
<b>Surgical</b>		
Ovarian cyst	4	12 to 18
Multiple fibroids	1	20
Chronic salpingitis	1	18
Ectopic pregnancy	3	18 to 24
Low transverse Caesarean section	9	32 to 48
Appendectomies during pregnancy	2	32 to 48
Panhysterectomy	4	48 to 55

(Chart adapted from Wager, H. P., et al.)\*

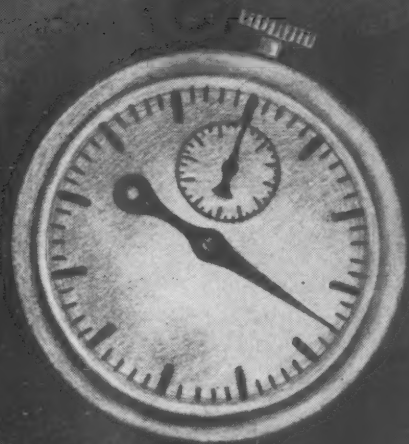
**Supplied:** COZYME in 10 ml. multiple dose vials containing 250 mg. per ml. of d-pantothenyl alcohol with 0.45% Phenol as preservative. COZYME 2 ml. single dose vial containing 250 mg. per ml. of d-pantothenyl alcohol. 25 vials per carton.

\*Wager, H. P., and Melosh, W. D.: West. J. Surg., 67:280,282 (Sept.-Oct.) 1959.

TRAVENOL LABORATORIES, INC. Morton Grove, Ill.

*in the postpartum patient*  
**COZYME™**  
 (d-pantothenyl alcohol, Travenol)  
*effectively prevents and corrects abdominal distention*





the critical  
fibrinogen  
index in  
60  
seconds



Ortho Pharmaceutical Corporation  
RARITAN, NEW JERSEY



**FOUND: a dependable solution to**

**"the commonest gynecologic office problem"**

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . ."

Ensey, J. E.: Am. J. Obst. 77:355, 1959

# TRICOFURON<sup>®</sup>

Improved

- Swiftly relieves itching, burning, malodor and leukorrhea
- Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis
- Achieves clinical and cultural cures where others fail
- Nonirritating and esthetically pleasing

## 2 steps to lasting relief:

1. **POWDER** for weekly insufflation in your office. MICOFUR<sup>®</sup>, brand of nifuroxime, 0.5% and FUROXONE<sup>®</sup>, brand of furazolidone, 0.1% in an acidic water-dispersible base.
2. **SUPPOSITORIES** for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

*Rx new box of 24 suppositories with applicator  
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**NITROFURANS**—a unique class of antimicrobials

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Q  
A

Why should I use  
**KANTREX®** Injection\*  
when there are  
so many other  
antibiotics available?

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics<sup>3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37</sup>

—organisms such as *Staph. aureus*, *Staph. albus*, *A. aerogenes*, *E. coli*, *H. pertussis*, *K. pneumoniae*, *Neisseria* sp., *Shigella*, *Salmonella* and many strains of *B. proteus*.

Q But if I use KANTREX Injection, won't that help make bacteria resistant to it also?

Next page, please .....

\*Kanamycin sulfate injection (Bristol)



**Q** *But if I use KANTREX Injection, won't that help make bacteria resistant to it also?*

**A** A very good question, but it is reassuring to note that in almost two years of clinical use of KANTREX for the treatment of infections for which it is recommended, the emergence of KANTREX-resistant bacterial populations has not been a problem.

**Q** *My impression is that KANTREX is just another neomycin. Isn't that so?*

**A** Indeed not. The only thing KANTREX and neomycin have in common is a similar antimicrobial spectrum. Otherwise, they're very different: they have different chemical structures; the toxicity of KANTREX is "much less than that of neomycin"<sup>14</sup>; and clinically, KANTREX Injection is practical for systemic administration routinely, while neomycin is not.

**Q** *You mean that KANTREX Injection doesn't have the nephrotoxicity of neomycin?*

**A** Precisely. It's true that when KANTREX Injection is used, urinary casts — even slight albuminuria or microscopic hematuria — may appear, especially in poorly hydrated patients, but this does not reflect any progressive damage to the kidneys. These signs promptly disappear on adequate hydration or termination of therapy.

**Q** *Then why do you recommend reduced dosage in patients with renal impairment?*

**A** Because renal impairment causes an excessive accumulation of KANTREX in the blood and tissues, when usual doses are administered. Since KANTREX Injection is excreted entirely by the kidneys, renal impairment leads

Q  
A



to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

**Q** *Is that why we see reports of patients developing hearing loss during KANTREX Injection therapy?*

**A** Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function — with minimal risk of ototoxicity.

**Q** *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use KANTREX Injection in such conditions?*

**A** Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus*, *A. aerogenes* and *E. coli*, even when renal impairment is present.

**Q** *What are the "proper precautions" in a patient with impaired renal function?*

**A** The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

**Q** *Why do you put so much emphasis on KANTREX's "rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

**A** There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.<sup>1, 2, 3, 7, 8, 9, 11, 15, 16, 19, 21, 22, 26, 29, 32, 33</sup> Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."<sup>29</sup>

**Q** *Does KANTREX Injection cause blood dyscrasias?*

**A** In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

**Q** *Can I administer KANTREX Injection in any other way than by the intramuscular route?*

**A** Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

**Q** *So you think I ought to use KANTREX Injection as my first choice antibiotic in staph and gram-negative infections?*

**A** Yes — because all evidence to date indicates that it is bactericidal against a wide range of organisms...rapid acting...does not encourage development of bacterial resistance...is well tolerated in specified dosage...and has not caused any blood dyscrasias.

## KANTREX<sup>®</sup> CAPSULES

*for local gastrointestinal therapy...  
not for systemic infections*

**Q** *Why can't I use KANTREX Capsules for systemic medication?*

**A** Because there is only negligible absorption of KANTREX from the gastrointestinal tract.<sup>3,5,6,8,28,34</sup> Thus, capsules cannot provide effective blood levels.

**Q** *Then what are KANTREX Capsules used for?*

**A** Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

**Q** *I've been using neomycin for preoperative bowel sterilization. Why should I switch to KANTREX Capsules?*

**A** Because KANTREX has been rated as "superior to neomycin" for this purpose.<sup>6</sup> It provides rapid and satisfactory control of coliforms, clostridia, staphylococci and streptococci; yeasts do not proliferate; stool concentrations of the drug are exceptionally high; and nausea, vomiting or intestinal irritation have not been observed.<sup>5,6</sup>

**Q** *What advantages do KANTREX Capsules offer me in the treatment of intestinal infections?*

**A** A high degree of effectiveness against most of the pathogens responsible for such infections: *Salmonella*, *Shigella*, *Staph. aureus*, *E. coli* and *Endamoeba histolytica*. Moreover, their use has been "remarkably free of any side effects."<sup>31</sup>

# KANTREX®

## INJECTION

KANAMYCIN SULFATE INJECTION

### INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

### DOSAGE: INTRAMUSCULAR ROUTE

Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

### TOXICITY

When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

### OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

### PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

### SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.

KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

## CAPSULES

(for local gastrointestinal therapy; not for systemic medication)

### INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

### PRECAUTION


Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

### SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

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A welcome clinical advance...  
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in an appealing form



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**SHORT DOSAGE SCHEDULE**—The short course of treatment with Milibis—only 10 suppositories in most cases—together with the clean, odorless, non-staining qualities eliminates psychic barriers which often interrupt longer treatments before complete cure.



SUPPLIED: BOXES OF 10  
with applicator.

Now supplied with  
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- SANITARY
- INSURES CORRECT  
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\*97 per cent effective in a study of 504 cases;  
94 per cent effective in a series of 510 cases.

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*"A number of our colleagues have insisted that (oxytocin) drip alone is adequate to produce these results. Our experience has convinced them that with the combined use of (oxytocin) and Cervilaxin, the remainder of the first stage, beyond an average of about 3.5 cm. dilatation is 43% to 51% less than with (oxytocin) alone."*<sup>1</sup>

CERVILAXIN® the highly purified, standardized preparation of relaxin—"third hormone of pregnancy"<sup>2</sup>—is indeed "a worthwhile adjunct to the medical induction of labor . . ."<sup>3</sup>

Given by intravenous drip, alone or with oxytocin, early in spontaneous or induced labor at term, CERVILAXIN acts physiologically and safely. It (1) softens the cervix, (2) eases delivery, by softening cervical and perineal tissues, and (3) avoids birth injuries, by diminishing cervical and perineal resistance to the expulsive forces of labor. In fact it makes the use of oxytocin safer as well as more efficient.

CERVILAXIN is supplied in 2-ml. vials containing 20 mg./ml., with detailed instructions for administration by intravenous drip.

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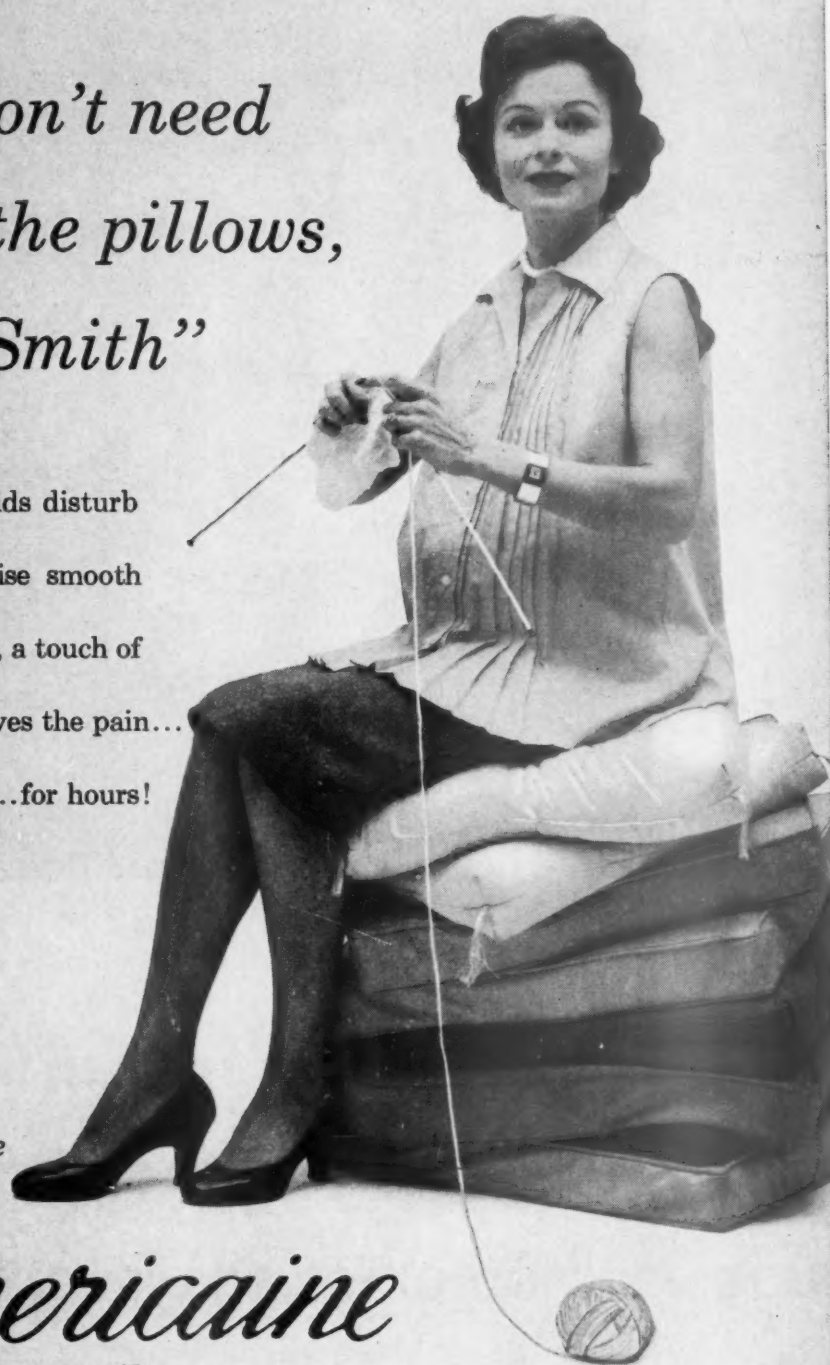
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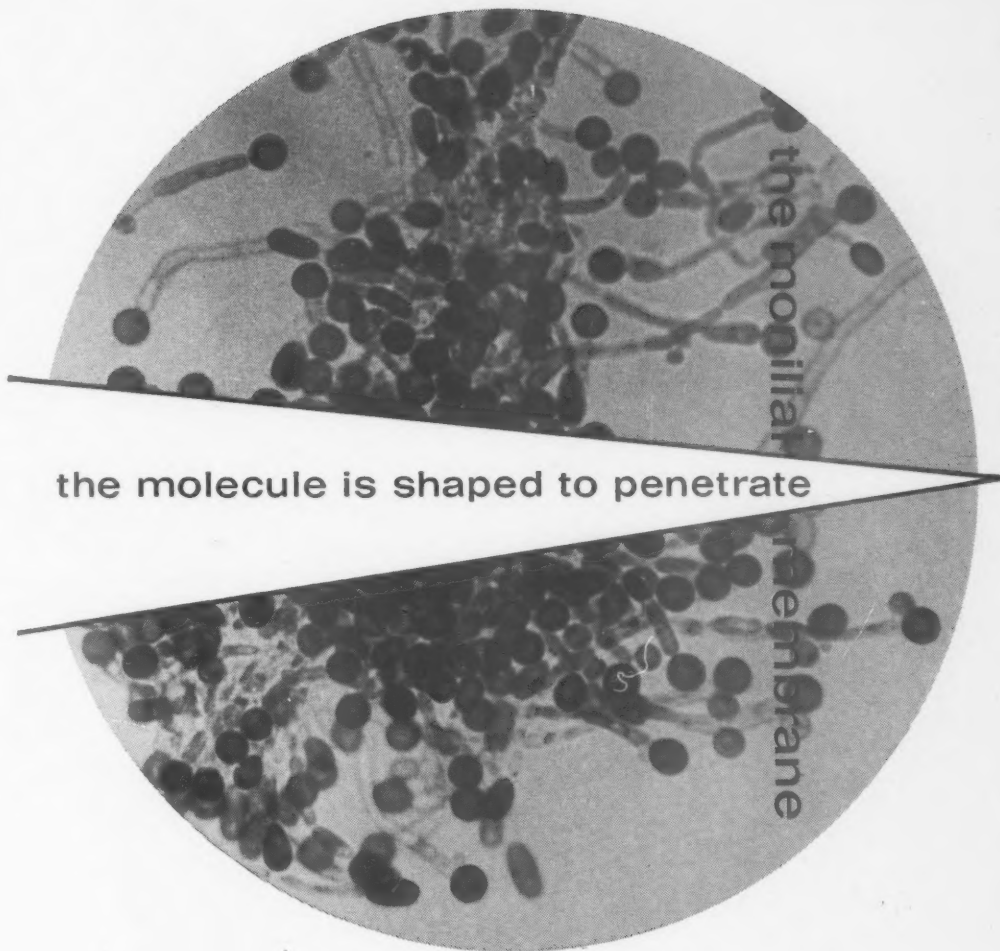


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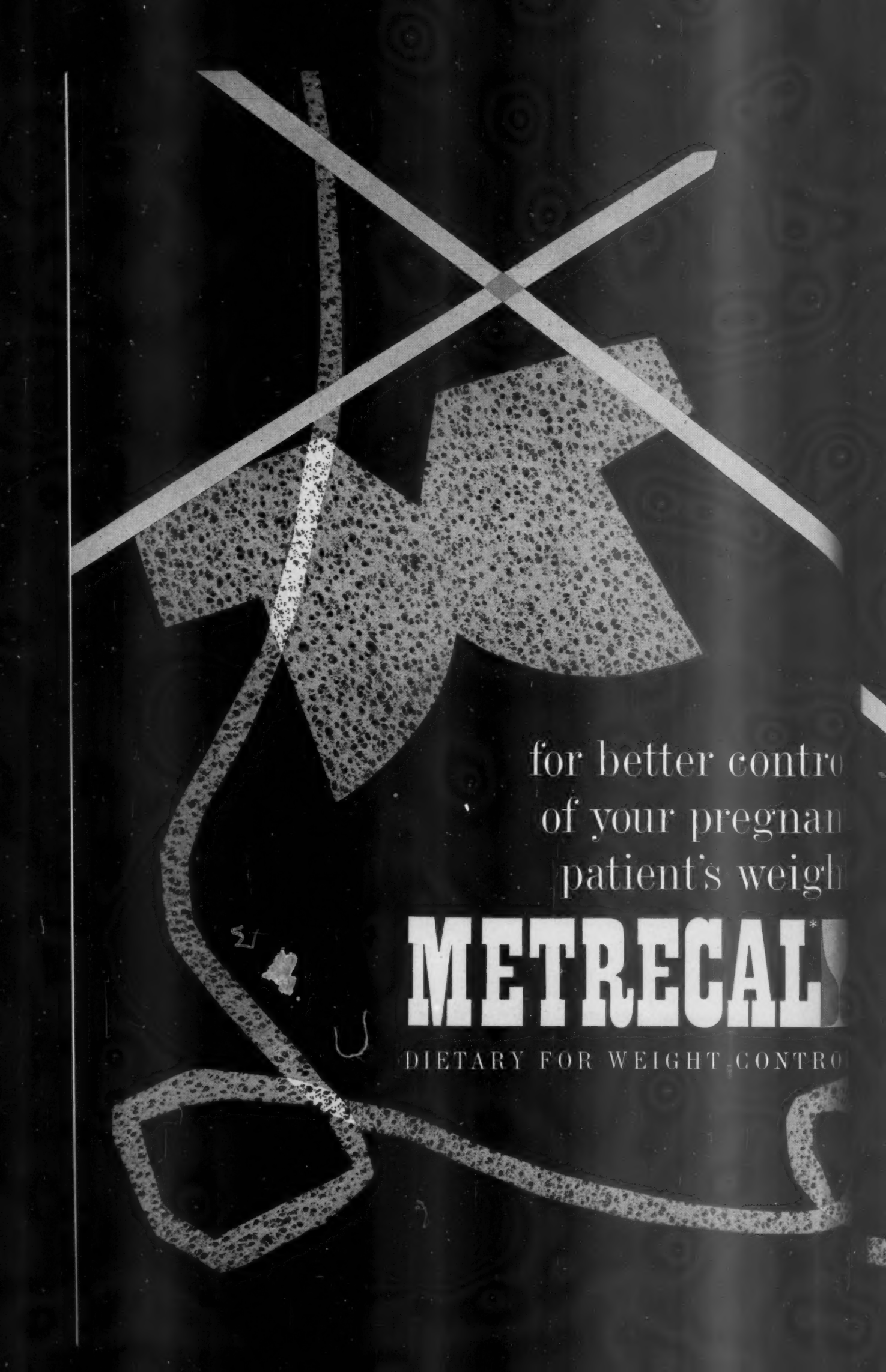
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\*Lapan, B.: Am. J. Obst. & Gynec. 78:1320, 1959.



An abstract black and white graphic. A large, light-colored 'X' is drawn across the frame. Below the 'X' is a large, irregular shape filled with a dense speckled pattern. A thin, light-colored line winds through the composition, passing behind the speckled shape and ending in a loop at the bottom left. The background is dark and textured.

for better control  
of your pregnant  
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*measured calories to help keep your patients at optimal weight levels...without appetite depressants*

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Metrecal may be used as the cornerstone around which to build a pregnancy diet when you wish to keep your patient's weight from rising too rapidly and to effect weight loss when necessary. A half-pound of Metrecal mixed with a quart of water supplies 900 calories in pleasant-tasting beverage form. This quantity provides 70 Gm. of protein, plus all essential vitamins and minerals. It is rich in calcium (2.0 Gm.) and iron (15 mg.). This daily ration may be divided into four glasses—one for each meal—and one at bedtime.

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***gratifying patient cooperation***

The high satiety, simplicity of use and palatability of Metrecal provide patients with a strong motivation to cooperate in weight-control programs.<sup>1,2</sup> Metrecal can provide a more dependable and nutritionally sound diet than the complex dietary schedules frequently used.

***no appetite depressants required***

Metrecal relies on sound nutritional principles for weight control rather than appetite depressants or diet "aids." Its pleasant taste and high satiety will help control the patient's appetite.

***easy to use—easy to prepare—variety of flavors***

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*Metrecal Weight-Control Guide is available from your Mead Johnson Representative or by writing to us, Evansville 21, Indiana.*

*References: (1) Antos, R. J.: Southwestern Med., 40:695-697 (Nov.) 1959. (2) Tullis, I. E., to be published.*



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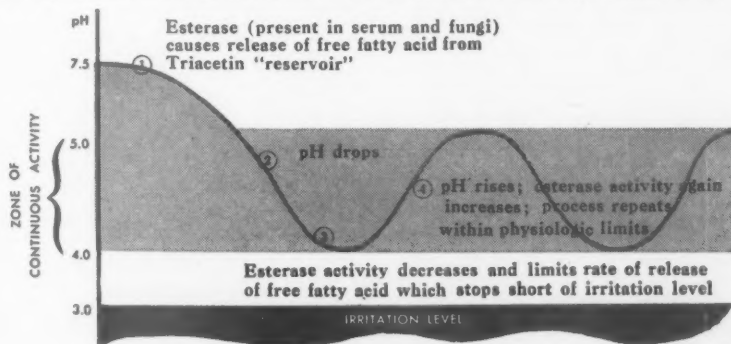
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**Usual Dosage:** 2 to 4 grams daily.

**Supplied:** No. 204-250 mg. Glyceryl triacetate per gram in a non-liquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

**References:** 1. Idson, B.: *Drug & Cosmetic Industry* 84:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, *Medical Records*, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: *Antibiotics & Chemotherapy*, to be published. 5. Knight, S. G.: *J. Invest. Dermat.* 28:363 (May) 1957. 6. Knight, S. G.: *Antibiotics & Chemotherapy* 7:172 (Apr.) 1957.



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Ferronord is so well tolerated that it may be given between meals. This is a great advantage—for two reasons. It saves the “iron-intolerant” patient the misery of gastric irritation, cramps and the other usual iron side effects. And the between-meal administration of Ferronord means greater utilization of this iron therapy because there is less interference with its gastric absorption. For your patients, these advantages are simply attained because Ferronord is as easy to prescribe as it is for patients to tolerate.



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*solves the old problems of oral iron therapy*

<i>Previous problem:</i>	<i>Ferronord solution:</i>
Oral forms didn't give high enough absorption	5 times greater absorption than ferrous sulfate <sup>1</sup>
Older oral forms too slow in eliciting response	Elevates serum iron in 3 hours; <sup>1</sup> maximum reticulocyte response in 5 to 9 days <sup>2</sup>
Older oral forms produced gastric upset, nausea, flatulence, constipation, etc., unless given with meals. But meals interfere with iron absorption.	Side effects "extremely rare"; <sup>3</sup> 95-98% of patients previously intolerant are Ferronord-tolerant. <sup>3</sup>

#### DOSAGE SCHEDULE

*For prophylaxis* (as in pregnancy)  
1-2 Ferronord Tablets (or 1-2 cc. Liquid)  
o.d. or b.i.d.

*For mild to moderate anemias*  
1 Ferronord Tablet (or 1 cc. Liquid) t.i.d.

*For severe anemias*  
2 Ferronord Tablets (or 2 cc. Liquid) t.i.d.

SUPPLY: *Tablets*, bottles of 100; *Liquid*, 60 cc. bottles with calibrated droppers. Each tablet (or cc.) contains 40 mg. of elemental iron.

*Bibliography:* 1. Feldman, H. S., and Clancy, J. B.: *Geriatrics* 13:517 (Aug.) 1958. 2. Pomeranze, J., and Gadek, R. J.: *New England J. Med.* 257:73 (July 11) 1957. 3. Clancy, J. B.: *Am. Pract. & Digest Treat.* 8:1948 (Dec.) 1957.

Ferronord<sup>®</sup>—brand of ferroglycine sulfate complex,  
U. S. Patent No. 2877253



NORDSON  
PHARMACEUTICAL  
LABORATORIES, INC.  
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ARE YOU  
ACHIEVING  
TRUE COLD  
STERILIZATION?

**WAREXIN<sup>\*</sup>**

IS LETHAL TO—**FUNGI, BACTERIA, VIRUSES, RESISTANT SPORES**—IN LESS THAN 1 HOUR—AND YET IS NON-TOXIC!



<sup>\*</sup>WAREXIN: Clorpactin<sup>®</sup> (a group of hypochlorous derivatives) to which buffers have been added for stability.

## PREVENT CROSS-INFECTION!

### Sterilize with WAREXIN

Can safely be used for:

1. All instruments made of stainless steel or other widely used corrosion-resistant alloys — even fine stainless hypodermic needles.
2. Articles made of rubber, plastic, non-porous fibers, glass, porcelain, enamel.
3. Complex equipment such as anaesthesia apparatus, heart-lung machines, artificial kidneys, etc.
4. Containers such as colostomy bags, urinals, air filters.
5. Special surfaces: hospital and laboratory walls, floors, tables.

## MIX WITH ORDINARY TAP WATER

Because Warexin concentrate is a *true* Cold Sterilizing Agent, it is unnecessary to use distilled water. Just add 1 level measure to each quart of tap water. Warexin solution gives you effective kill in 1 hour or less.

**ECONOMICAL!** A 5 oz. bottle makes 12-16 quarts of solution. Cost: approximately 27¢ a quart!



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Lattimer, John K., and Spirito, A. L.: Clorpactin for Tuberculosis cystitis: Instrument sterilization, *Journ. of Urology*, Vol. 73, No. 6, June, 1955. • Wolinsky, E., Smith, M. M. and Steenken, Wm. Jr., Tuberculocidal Activity of Clorpactin. A New Chlorine Compound, *Antibiotic Medicine*, 1:382-384, July, 1955. • Sanders, Murray and Soret, M. G.: Virucidal activity of WCS-90, *Antibiotics and Chemotherapy*, Vol. V, No. 11, Nov. 1955. • Gliedman, M. L., Lt. (MC) USNR, Grant, R. N. Capt. (MC) USN, Vestal, B.L., B.S., and Karlson, K.E., M.D.; Impromptu Bowel Cleansing and Sterilization, *Surgery*, 43:282-287. • From The Textbook, Extracorporeal Circulation, Edited by Dr. J. Garrott Allen, Page 87; Charles C. Thomas, Publisher.

# IN NAUSEA AND VOMITING OF PREGNANCY

# USE

## SPECIFIC

Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage

## ESTABLISHED

6-year record of successful use in daily practice; consistently favorable reports<sup>1-10</sup>

## UNCOMPLICATED

Has no known contraindications; free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines

# BONINE

brand of meclizine hydrochloride

**FORMERLY BONAMINE**

## SUPPLIED:

**BONINE** Tablets, scored, 25 mg.

**BONINE** Chewing Tablets, mint-flavored, 25 mg.

**BONINE** Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).

**DOSAGE:** Adults, 25 to 50 mg. once a day.

## BONINE REFERENCES:

1. Moyer, J. H.: M. Clin. North America, Mar. 1957, p. 405.
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## a brighter outlook—for the whole day

To relieve the constipation of pregnancy, expectant mothers especially appreciate the effectiveness and convenience of pleasant-tasting Agoral. Taken at bedtime this gentle laxative works overnight, without disturbing sleep, to produce a normal bowel movement next morning—helps meet nature's need *before* the active day begins. In the hospital, too, your postpartum patients and their busy nurses will appreciate the many advantages of Agoral.

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*the gentle laxative*

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THE CLASSICAL TREATMENT FOR VAGINAL MONILIASIS

# HYVA GENTIAN VIOLET VAGINAL TABLETS

*the only*  
SPECIFIC ANTIMYCOTIC  
VAGINAL TABLET WITH  
A GEL FORMING BASE

A vaginal therapy: Methylrosaniline chloride (gentian violet) has generally proved the most effective and specific agent for the treatment of vaginal candidiasis caused by the fungus *Candida*.

Hyva Gentian Violet Tablets virtually eliminate the principal disadvantages of present gentian violet preparations. They may be handled and used without staining and have psychological and aesthetic acceptance.

Hyva combines the fungicidal action of gentian violet (1.0 mgm.) with three active surface reducing agents and bactericides.\*

These active ingredients have been incorporated into a mildly effervescent "gel" forming base which provides for maximum and prolonged effectiveness. Shorter treatment time is required without the usual messiness normally experienced.

One tablet intravaginally for 12 nights. When necessary one tablet twice daily may be recommended. Patient should take a Nylmerate Solution water douche on arising and preceding next tablet application.

Prescribe Hyva Gentian Violet Tablets with applicator—boxes of 12 tablets.

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\*Alkyldimethylbenzylammonium chloride  
(0.5 mgm.)  
Polyoxyethylenenonylphenol (10.0 mgm.)  
Polyethylene Glycol Tert-Dodecylthioether  
(5.0 mgm.)



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**CASE NO. 1**

Blood Coagulation Time  
3 min. 15 sec.  
Bleeding Time . 1 min. 30 sec.

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Blood Coagulation Time  
3 min. 25 sec.  
Bleeding Time . 1 min. 20 sec.

**CASE NO. 3**

Blood Coagulation Time . 3 min.  
Bleeding Time . 1 min. 30 sec.

**CASE NO. 4**

Blood Coagulation Time  
3 min. 15 sec.  
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Blood Coagulation Time  
3 min. 10 sec.  
Bleeding Time . 1 min. 40 sec.

All had normal blood studies—  
yet one had a bleeding problem.



1



2



3



4



5

**Adrenosem<sup>®\*</sup>**  
SALICYLATE  
(Brand of carbazochrome salicylate)

\*U.S. Pat. Nos. 2581850, 2506294

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Bristol, Tennessee • New York • Kansas City • San Francisco



# Adrenosem<sup>®</sup>

SALICYLATE  
(Brand of carbazochrome salicylate)

## TO CONTROL THE MOST COMMON CAUSE OF BLEEDING

The most common cause of bleeding is increased capillary permeability, according to recent studies. Coagulative defects, the least common cause, occurred in less than one of every four patients whose chief complaint was abnormal bleeding.\*

Without a history of bleeding, there is no way of determining whether a patient tends to exhibit increased capillary permeability. Therefore many surgeons administer Adrenosem preoperatively as a standard safety measure.

Adrenosem controls bleeding by decreasing excessive capillary permeability and promoting retraction of severed capillary ends. Thus it controls the chief cause of bleeding. Its high index of safety, with no contraindications at recommended dosage levels, establishes Adrenosem as a standard preventive measure, even where there is no history of abnormal bleeding.†

### A VALUABLE ADJUNCT TO SURGERY

The preoperative use of Adrenosem adds an extra measure of safety during surgical procedures. It makes good technic even better, by providing a clear operative field.



\*E. Cheraskin:  
The Control of Bleeding,  
J. Am. Dent. Assn.,  
58:17 (Apr., 1959).

†Extensive bibliography  
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### SUPPLIED:

AMPULS—1 cc., 5 mg.

TABLETS—1 and 2.5 mg.

SYRUP—each 5 cc., 2.5 mg.

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any  
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while they are planning  
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they need your help  
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the most widely prescribed contraceptive

**WHENEVER A DIAPHRAGM IS INDICATED**



# When there's a pram in her future,

So you've given her the news she's been waiting to hear. And fixed her up with a new regimen. What then, Doctor? That isn't the end of it, is it? ■ More often than not, your pregnant patient will be in need of *added* nutritional support. This is when you might consider new Pramilets. Each Pramilet Filmstab is rich in phosphorus-free calcium, iron, plus those other nutrients so important when the maternal nutritional reserves are to be taxed. ■ In prescribing Pramilets you're not only giving the mother-to-be everything she needs in a prenatal supplement—you're giving her the easiest dosage schedule imaginable, just one a day in many cases. Pramilets, pink and pretty, in slim, graceful Table Bottles of 100.

she'll need

**Pramilets** FILMTAB to

*Comprehensive vitamin-mineral support with just 1 Filmstab daily.*



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in constipation during  
pregnancy and postpartum

# KONDREMUL<sup>®</sup>

micromulsion bowel regulator

Patch

## a move in the right direction

The gentle, predictable action of KONDREMUL provides a safe, effective approach to the problem of constipation during pregnancy and postpartum. KONDREMUL establishes regularity without danger of laxative habituation . . . induces soft, easily evacuated stools to avoid strain and injury to hemorrhoids or anal fissures. In postpartum patients, KONDREMUL obviates the need for enemas.

KONDREMUL, the delicious micromulsive mineral oil encapsulated in Irish Moss, leaves no oily aftertaste and mixes readily with hot or cold beverages. KONDREMUL does not interfere with vitamin absorption.

## Available in 3 forms

KONDREMUL Plain

KONDREMUL with Cascara

KONDREMUL with Phenolphthalein

Write today for a free supply of "A Guide to Normal Bowel Function." The pamphlet offers suggestions to patients to help them cooperate with therapy and thus help themselves maintain normal bowel function.

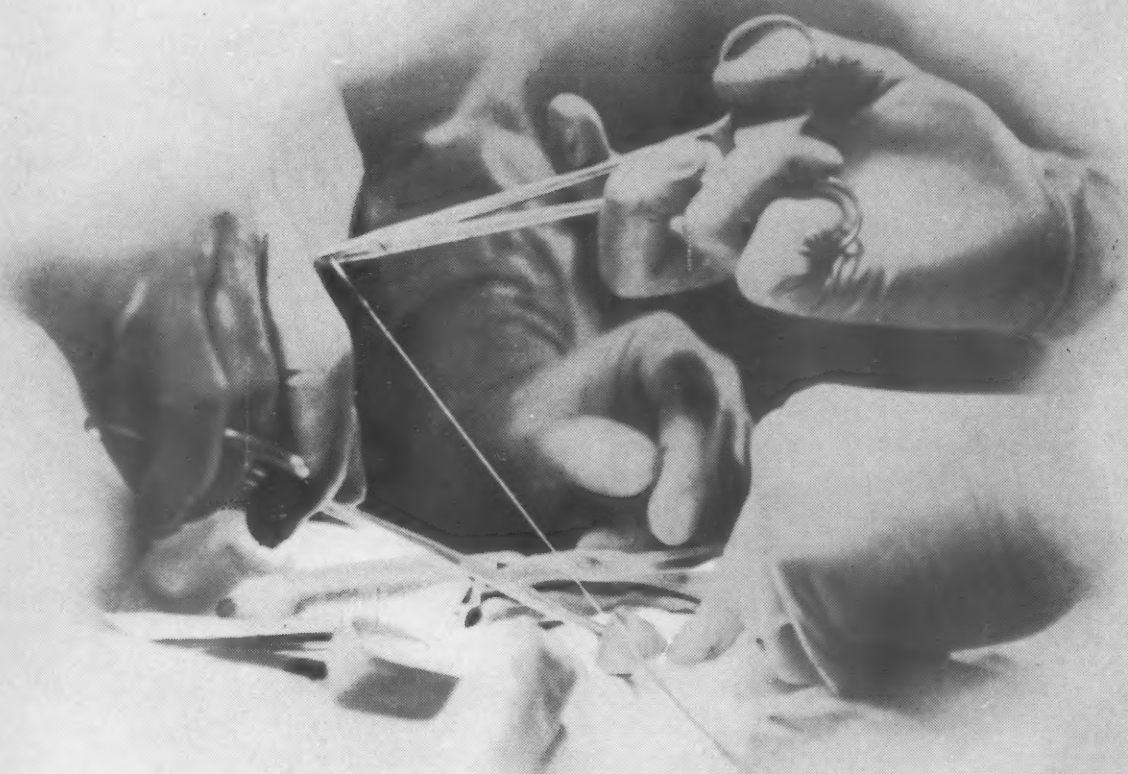


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INJECTION  
TABLETS  
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SUPPOSITORIES

## new hope for fetal salvage

# DELALUTIN

The results of administering Delalutin before the 12th week of gestation to 82 women with habitual abortion were reported recently by Reifstein<sup>1</sup> in a compilation of data supplied by 45 investigators. Every patient had experienced at least three consecutive abortions immediately preceding the treated pregnancy. More than 68% of these women were delivered successfully and uneventfully following Delalutin therapy.

Boschann,<sup>2</sup> in a study of pregnancies with threatened abortion, found that:

37% of 73 pregnancies were carried to term without progestational therapy

64% of 42 pregnancies were salvaged by progesterone

83% of 73 pregnancies were salvaged by Delalutin

Eichner,<sup>3</sup> found that in Delalutin-treated women, fetal salvage of infants below term

weight (1000 to 2000 gm.) was significantly improved. 108 (76%) of 142 babies of this birth weight survived without mothers receiving progestational therapy, while 16 (100%) of 16 babies of this birth weight survived with mothers receiving Delalutin therapy. A comparison study was made of a group of repeated aborters treated with Delalutin, and a group with a similar history treated with bed rest and sedation.<sup>4</sup> Pregnancy salvage with Delalutin was twice that of the control group. Delalutin was found to be "highly active", well-tolerated and long-acting.

According to Tyler and Olson,<sup>5</sup> "These qualities of prolonged action and relative freedom from local reactions make [Delalutin] a generally more desirable therapeutic agent for intramuscular use than progesterone . . ."

### DELALUTIN BABIES WHOSE MOTHERS WERE HABITUAL ABORTERS



Mary Ann Cribben  
Garden City, N. Y.



Amy Sue Greenman  
Lincolnwood, Ill.



William Peller  
Skokie, Ill.



Randy Sinis  
Denver, Colo.



Richard Miller  
Denver, Colo.



Scott Knudsen  
Norwich, Vt.

References: 1. Reifstein, E. C. Jr.: *Annals N. Y. Acad. Sc.* 71:762 (July 30) 1958. 2. Boschann, H.-W.: *ibid.*, p. 727. 3. Eichner, E.: *ibid.*, p. 787. 4. Hodgkinson, C. P.; Igna, E. J., and Bukeavich, A. P.: *Am. J. Obst. & Gynec.* 76:279, 1958. 5. Tyler, E. T., and Olson, H. J.: *J.A.M.A.* 169:1843, 1959.

# DELALUTIN <sup>improved</sup> <sup>progestational</sup> <sup>therapy</sup>

SQUIBB HYDROXYPROGESTERONE CAPROATE

*DELALUTIN offers these advantages over other progestational agents:*

- long-acting sustained therapy
- more effective in producing and maintaining a completely matured secretory endometrium
- no androgenic effect
- more concentrated solution requiring injection of less vehicle
- unusually well-tolerated, even in large doses
- fewer injections required
- low viscosity makes administration easier

DELALUTIN is also potent and safe therapy for: threatened abortion; postpartum after-pains; amenorrhea, primary and secondary; dysfunctional uterine bleeding not associated with genital malignancy; infertility with inadequate corpus luteum function; production of secretory endometrium and desquamation during estrogen therapy; premenstrual tension; dysmenorrhea; cyclomastopathy, mastodynia, adenosis and chronic cystic mastitis.

#### *Administration and dosage:*

Because of its low viscosity, Delalutin may be administered with a small gauge needle (deep intragluteal injection). Complete information on administration and dosage is supplied in the package insert.

#### *Supply:*

Delalutin is available in vials of 2 and 10 cc., each containing 125 mg. of hydroxyprogesterone caproate in sesame oil, and benzyl benzoate.

*Each of these healthy, normal babies was born by a mother with a documented previous history of true habitual abortion, who was treated during her most recent pregnancy with DELALUTIN.*



Nina Rutkowski  
Roselle, Ill.



Rosanne Guberman  
Elmont, L.I., N. Y.



Kenneth Michael Simonson  
Denver, Colo.



Joanne Verderosa  
Seaford, N. Y.



J. Gettemy  
Hartford, Conn.



Karen Mary Nederman  
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for your problem overweight patients

## NEW ESKATROL\* SPANSULE®

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a logical combination of Dexedrine® (*brand of dextro amphetamine*) and Compazine® (*brand of prochlorperazine*) that

1. curbs the appetite
2. relieves the underlying psychic stress
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with a negligible incidence of restlessness and insomnia

Dosage: One capsule in the morning.  
Prescription Size: Bottles of 30 capsules.

**SMITH  
KLINE &  
FRENCH**

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more closely approaches the ideal diuretic



"When compared to other members of this heterocyclic group of compounds, this drug [NATURETIN] shows a significantly increased natriuresis and decreased loss of potassium and bicarbonate. In this respect it more closely approaches a natural or 'ideal diuretic.' It is effective upon continuous administration and causes no significant serum biochemical changes. It is effective in a wide variety of edematous and hypertensive states and represents a significant advance in diuretic therapy." *Ford, R.V.: Pharmacological observations on a more potent benzothiadiazine diuretic; accepted for publication by the American Heart Journal.*

# Naturet̄in

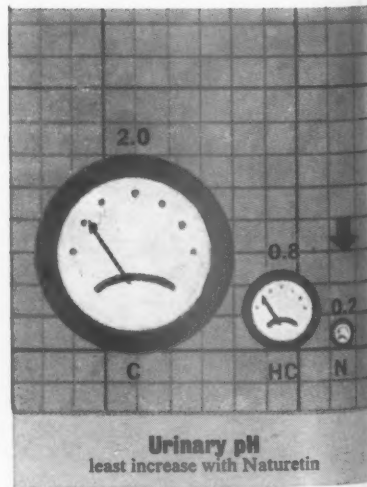
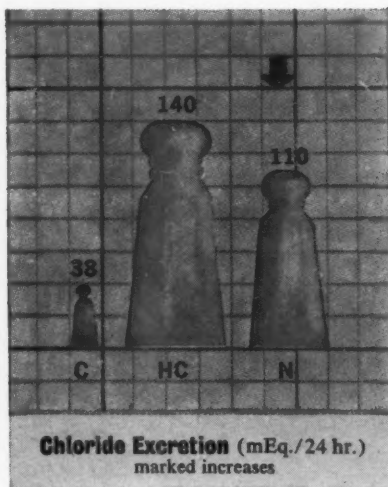
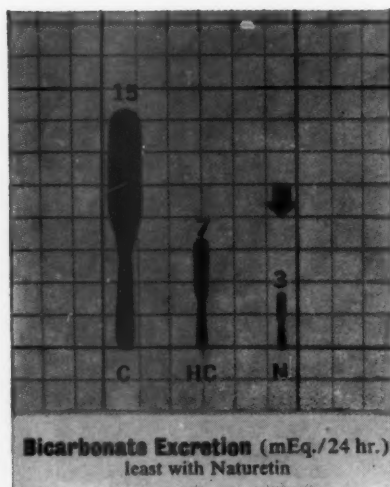
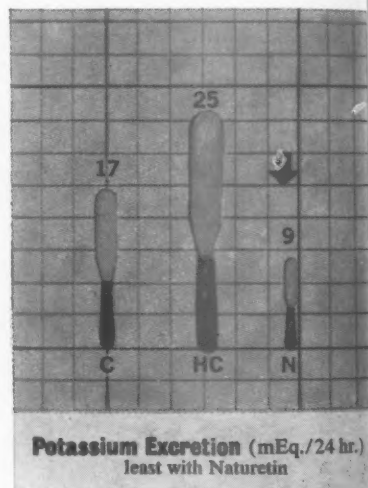
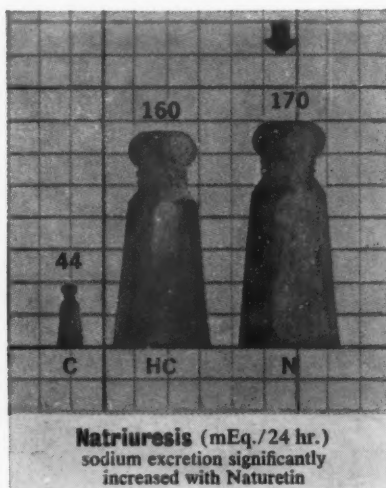
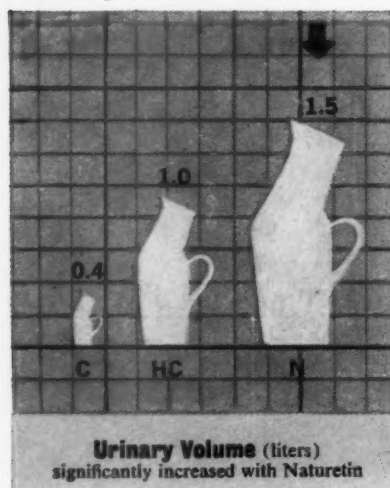
Squibb Benzydrolumethiazide

# Naturetin

Squibb Benzydrolumethiazide

more closely approaches the ideal diuretic

Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydrolumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

## a single 5 mg. tablet once a day provides all these advantages<sup>2</sup>

- prolonged action — in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage — more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.—more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity — few side effects — low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other anti-hypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

<sup>2</sup>Reports (1959) to the Squibb Institute for Medical Research.

**Naturetin** — *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

*Contraindications:* none, except in complete renal shutdown.

*Precautions:* when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs — leg or abdominal cramps, pruritus, paresthesia, rash — suggestive of hypersensitivity, are noted.

**Naturetin** — *Dosage:* in edema, average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. In hypertension: suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

**Naturetin** — *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

SQUIBB



Squibb Quality —  
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Ingredient

Rx Naturetin 5mg.  
Disp. #30  
Sig: 1 each morning.

<sup>1</sup>RAUDIXIN<sup>®</sup> AND <sup>2</sup>NATURETIN<sup>®</sup> ARE SQUIBB TRADEMARKS.

*Emphasizes Application of Physiology  
To Routine Practice of Medicine*

10th Edition

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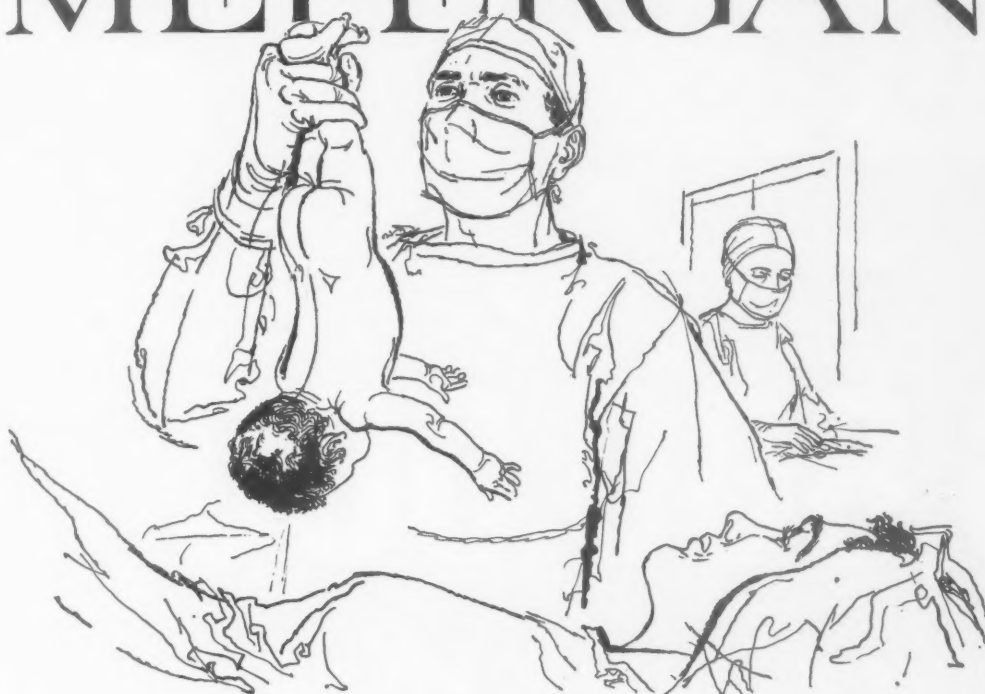




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childbirth  
...and reduced risks  
for infants

*analgesia with a plus*

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With MEPERGAN as a part of management, obstetrical patients are usually relaxed, free of apprehension, and sleep quietly between their pains. Awakened easily, they are mentally alert and cooperative. Multiparae frequently report that the discomfort of labor is less than on previous occasions. Labor is often shortened. Nausea and vomiting are rare. The anesthetic course is smooth. And, most important, there is decreased hazard of hypoxia for both mother and infant. Widespread clinical experience points to MEPERGAN's 1:1 ratio of promethazine and meperidine to be most satisfactory for most patients.

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*See package circular for complete information on use of MEPERGAN.*

MEPERGAN is the registered trademark for Promethazine Hydrochloride and Meperidine Hydrochloride, Wyeth.



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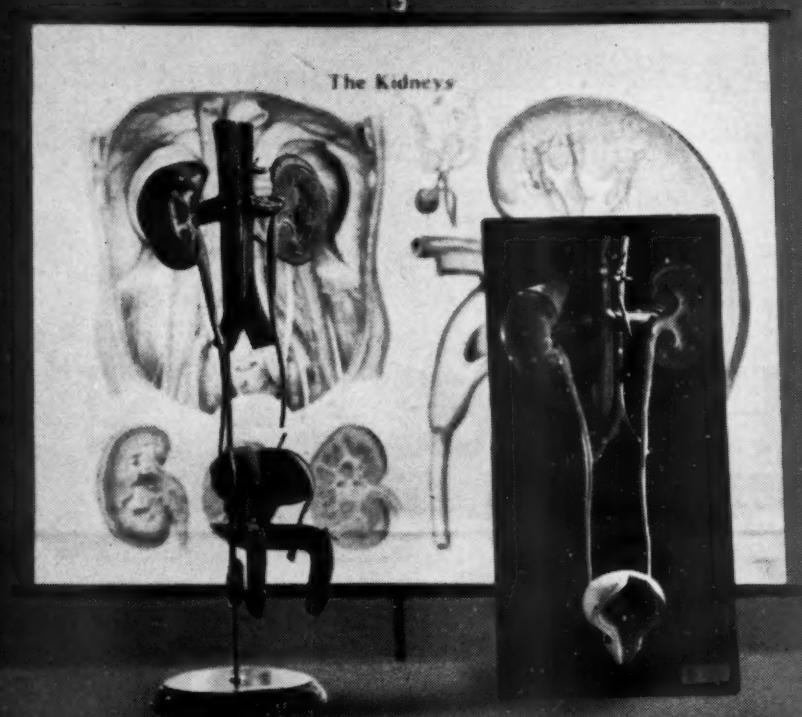


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**courses of treatment\* and still negligible  
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**in genitourinary tract infections**

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### OVER-ALL RESPONSE OF GRAM-NEGATIVE BACTERIA TO ANTIMICROBIAL DRUGS<sup>3</sup>

	No. organisms tested	No. sensitive (%)	No. moderately resistant (%)	No. resistant (%)
Nitrofurantoin	1730	1074 (62.1%)	—	656 (37.9%)
Tetracycline	2879	1000 (34.7%)	434 (15.1%)	1445 (50.2%)
Chloramphenicol	2879	1268 (44.0%)	725 (25.2%)	886 (30.8%)
Streptomycin	2879	943 (32.8%)	368 (12.8%)	1568 (54.4%)
Sulfisoxazole	1730	452 (26.1%)	—	1278 (73.9%)

"In order of decreasing effectiveness, the activity of the drugs against gram-negative organisms was as follows: nitrofurantoin, chloramphenicol, tetracycline, streptomycin, and sulfisoxazole."

### OVER-ALL RESPONSE OF GRAM-POSITIVE BACTERIA TO ANTIMICROBIAL DRUGS<sup>3</sup>

	No. organisms tested	No. sensitive (%)	No. moderately resistant (%)	No. resistant (%)
Nitrofurantoin	320	289 (90.3%)	—	31 ( 9.7%)
Penicillin	2353	515 (21.9%)	308 (12.9%)	1535 (65.2%)
Erythromycin	2353	1633 (69.4%)	308 (13.1%)	412 (17.5%)
Tetracycline	2353	987 (41.9%)	673 (28.6%)	693 (29.5%)
Chloramphenicol	1939	1593 (82.2%)	242 (12.5%)	104 ( 5.3%)
Sulfisoxazole	303	25 ( 8.3%)	—	278 (91.7%)

"For the gram-positive organisms, the order of decreasing effectiveness was: nitrofurantoin, chloramphenicol, erythromycin, tetracycline, penicillin, and sulfisoxazole, although relatively few strains were tested against the first and last drugs."

Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

References: 1. Seneca, H., and Lattimer, J. K.: A.M.A. Arch. Path. 64:481, 1957. 2. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 95:653, 1955. 3. Metzger, W. I.: Antibiotics Annual 1958-1959, edited by H. Welch and F. Marti-Ibanez, New York, Medical Encyclopedia, Inc., 1959, pp. 966-971.

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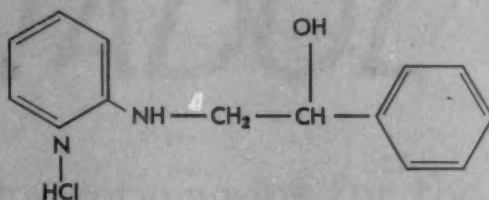
# analexin



**therefore...in pain...  
where pain makes tension  
and tension makes pain...  
analexin stops both effectively**

**A** Analgin is a new synthetic chemical (phenylamidol hydrochloride) that inherently possesses within one molecular structure two different pharmacologic actions: (1) *general analgesia*, by raising the pain threshold and thus decreasing the perception of pain, and (2) *muscle relaxation*, by selectively depressing subcortical, brain stem and spinal polysynaptic transmission (interneuronal blockade), abolishing abnormal muscle tone without impairing normal neuromuscular function.<sup>1,2</sup>

**A** Although the analgesic potency of one tablet is clinically equivalent to one grain of codeine, Analgin is not narcotic or narcotic related. It is not habituating and tolerance to the drug has not been noted. Muscle relaxant action is comparable to the most potent muscle relaxants available for oral use. *The total effect is "analgomyxation"—a new advance for the relief of pain.*



The full chemical name for phenylamidol is 2-( $\beta$ hydroxyphenethylamino)-pyridine hydrochloride. It is unrelated to any currently available analgesic or muscle relaxant compound.<sup>3,4</sup>

*Heisler*

## **analexin provides effective relief of the total pain experience...**

**A** The end result of pain, regardless of its origin, is discomfort or suffering paralleled by muscle tension. Thus muscle tension may play a fundamental role in the total pain experience even though it does not initiate the pain. Employment of a single agent that produces two distinct but associated physiologic responses has obvious advantages, for relief of the total pain experience is better accomplished by the integrated action of phenylramidol which acts on both pain centers and muscle to produce analgesia and relieve muscle tension simultaneously.

## **with remarkably few side effects**

**A** Side effects such as sedation, euphoria, mental confusion and depression, sometimes associated with inter-neuronal blocking and certain analgesic agents have not been noted with Anallexin. Incidence of reactions is low and those reactions that occasionally occur (such as gastric irritation and pruritus) are of a mild and transient nature and do not limit therapy.<sup>5</sup>

**NEIAPR**

anallexin



*announcing a new class of drug*

3

## **results with analexin in clinical trials**

Batterman, Grossman and Mouratoff<sup>5</sup> compared Anallexin with aspirin, sodium salicylate and a placebo in a series of 195 patients with various painful conditions. The authors concluded:

"Not only is satisfactory relief of painful states achieved in the majority of patients regardless of etiology and duration of pain, but there is also no evidence suggestive of cumulative toxicity. Furthermore, in contrast to codeine and meperidine, the likelihood of untoward reactions occurring in ambulant patients is not high. This is a decided advantage since the control of pain in the ambulant patient with chronic pain is a major clinical problem."

"Phenylramidol (Anallexin), with therapeutic doses is not only safe for chronic administration, but also to date we have noted no adverse effect upon the cardiovascular, gastrointestinal, respiratory, kidney, liver or central nervous systems."

Wainer<sup>6</sup> reported a series of 200 cases treated with phenylramidol for various painful conditions. In fifty of these patients who had dysmenorrhea, he saw excellent results in 40, good results in 5 and poor results in 5. Further examination in 4 cases not responding revealed presence of organic pathology. A second group of 50 cases with headache and associated premenstrual tension responded with over-all excellent results. Wainer also reports the use of phenylramidol to replace codeine for postpartum pain and describes 100 cases wherein a combination of phenylramidol with aluminum aspirin (Anallexin-AF) successfully replaced aspirin and codeine therapy.

*Neisler*

**anallexin**





## more results with analgin in clinical trials

⌘ In another series of dysmenorrhea cases, Bader<sup>7</sup> compiled data on 20 employees of a telephone company who required ½ to 2 days off from work every month regardless of prior therapy employed. Satisfactory results were achieved in 15 out of 20 and a fair response in the remaining five. All were able to remain on the job although relief was not complete in the latter cases.

⌘ Bealer<sup>8</sup> treated 32 patients with phenylramidol mostly for musculoskeletal disorders and had good or very good results in 15, fair results in 14 and poor or inconclusive results in 2 patients. Cohen<sup>9</sup> used phenylramidol together with aspirin in 15 patients with such conditions as sciatic pain, osteoarthritis, anterior chest wall syndrome, etc. and got outstanding relief in 80 per cent. Gilbert<sup>10</sup> reported that 15 patients with nonspecific headache had excellent relief in a matter of minutes with phenylramidol, and in 8 cases of dry socket pain Bruno<sup>11</sup> reports immediate relief in six cases and good results later in the other two after sockets were curetted under local anesthesia. Stern<sup>12</sup> reported on 40 ambulatory cases with a variety of painful conditions and saw good relief in 32 patients and poor in 8. Results were best in acute sacroiliac pain, myositis, muscle spasm, fractures, pleurisy and neuritis. Ten of 13 patients with osteoarthritis responded very well and are continuing on phenylramidol therapy.

Bealer

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genitourinary conditions  
(premenstrual cramping or tension)  
abdominal distress  
(flatulence, colic)  
toothache and dry socket pain

**analexin-AF** (phenylramidol with aluminum aspirin)

for relief of pain and muscle tension also

involving inflammatory processes and/or fever, as in:

arthritis  
arthralgia  
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myalgia of strain and tear  
pre- and postoperative toothache

dosage:

**analexin:** for relieving pain and/or muscle tension, one or two tablets every 4 hours. In dysmenorrhea, two tablets initially then one tablet every 2 to 4 hours as needed.

**analexin-AF:** two tablets every 4 hours or as required.

supply:

**analexin tablets**—Each tablet contains 200 mg. of phenylramidol HCl. Bottles of 100 tablets.

**analexin-AF tablets** — Each tablet contains 100 mg. of phenylramidol HCl and 300 mg. of aluminum aspirin. Bottles of 100 tablets.

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
Clinical Reports cited above are in the files of the Medical Department, Irwin, Neisler & Co.

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<sup>†</sup>Data calculated from: Watt, B. K. et al., U.S. Dept. Agric. Handbook No. 8, 1950; and Burger, M. et al. Agr. & Food Chem. 4:418, 1956.

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#### **References:**

- (1) Barnes, R. H.: J.A.M.A. 166:898, 1958. (2) Ressler, C.: J.A.M.A. 165:135, 1957.  
(3) Birnberg, C. H., and Abitbol, M. M.: Obst. & Gynec. 11:463, 1958. (4) Robillard, R.: Canad. M.A.J. 76:938, 1957.

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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

\*Experimental dosage (see dosage recommendations adjacent)

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1. Rosenfield, H. H., et al.: *Obst. & Gynec.* 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: *Textbook of Obstetrics and Obstetric Nursing*, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Heltman, L. D.: *Gastroenterology*.

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**References:** 1. Peikes, I. L.: Journal-Lancet 79:368, 1959. 2. Cacciarelli, R. A.: J. M. Soc. New Jersey 46:87, 1949. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 6. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 7. Cicalese, G.: Personal communication. 8. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946. 9. Crisp, W. E.: Personal communication. 10. Parks, J.: M. Ann. District of Columbia 12:175, 1943. 11. Kroger, W. S.: Personal communication. 12. Peikes, I. L.: In press.

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## American Journal of Obstetrics and Gynecology

### OBSTETRICS

## The electronic evaluation of fetal heart rate

### II. Changes with maternal hypotension

EDWARD H. HON, M.D.\*

BEVAN L. REID, M.B.B.S.\*\*

FREDERICK W. HEHRE, M.D.

*New Haven, Connecticut*

THE association of fetal bradycardia and maternal hypotension is well known in clinical obstetrics. Hingson and Hellman<sup>1</sup> state that "fetal bradycardia develops invariably within five minutes after the maternal blood pressure has fallen below 80 mm. of mercury, systolic pressure." While the signifi-

cance of this type of bradycardia is not known, in their study of 7,445 infants delivered by both inhalation and regional methods of anesthesia, there was a direct relationship between the magnitude of the drop in maternal systolic blood pressure and delayed crying time. They also encountered an "unexpected" high incidence of fetal loss in premature infants with spinal anesthesia. However, the total perinatal mortality in the group which received inhalation anesthesia did not differ significantly from that in the group receiving regional anesthesia.

The significance of moderate degrees of maternal hypotension may not be reflected in the perinatal mortality rate since lesser degrees of fetal damage may be manifested by various central nervous system lesions appearing in later life. On the other hand,

*From the Department of Obstetrics and Gynecology and the Department of Anesthesiology Yale University School of Medicine.*

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*\*Markle Scholar in Medical Science.*

*\*\*Visitor from the University of Sydney, Sydney, Australia.*

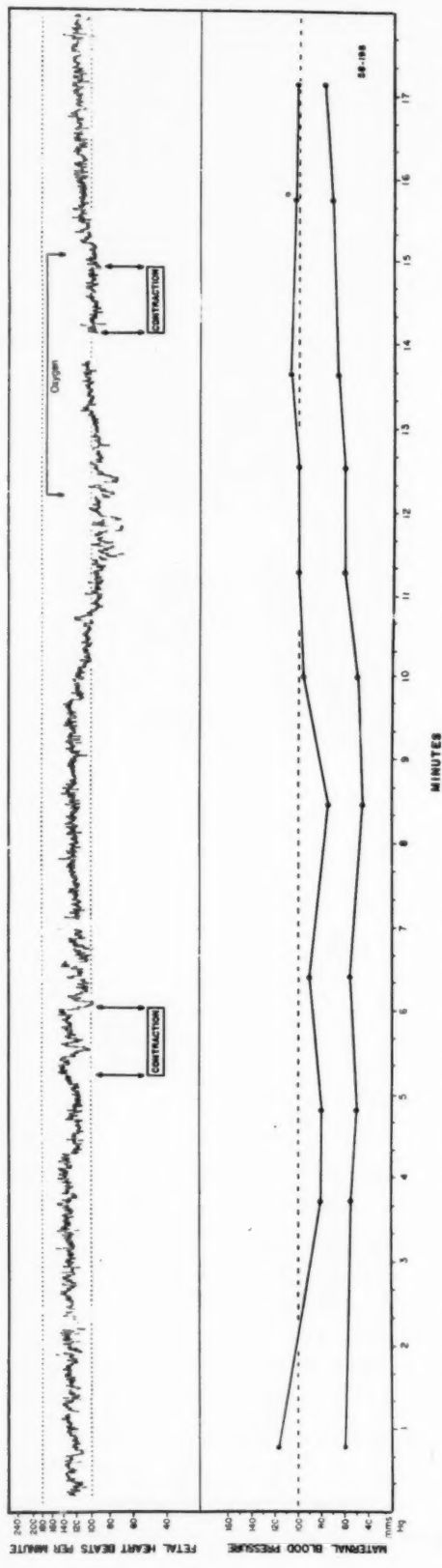


Fig. 1. Fetal bradycardia associated with maternal hypotension. Note 5 minute delay in the onset of fetal bradycardia following hypotension and a similar delay in return to normal following return to normotension.

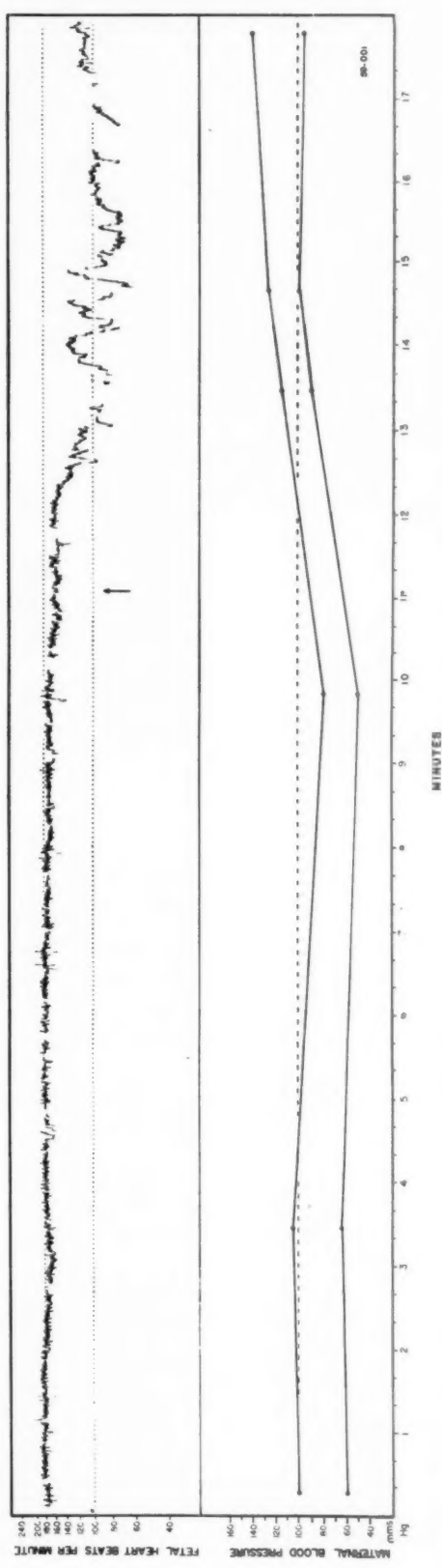


Fig. 2. Fetal bradycardia associated with hypotension at the time of repeat cesarean section (peridural anesthesia). The arrow indicates the intramuscular injection of a vasopressor.



there is little doubt that if maternal hypotension is sufficiently severe and prolonged the fetus will die.<sup>2</sup>

For many years adequate maternal arterial blood pressure has been considered essential for maintaining blood flow through the intervillous space. In the presence of hypotension, there is a decrease in blood flow and resultant fetal hypoxia.<sup>1, 3-6</sup>

In a recent report,<sup>7</sup> an attempt was made to differentiate the fetal bradycardia pattern due to umbilical cord compression, which may be due largely to vascular reflexes as well as to hypoxia, from that due to fetal hypoxia primarily. This report describes fetal heart rate patterns observed during episodes of maternal hypotension and compares them with patterns of "pathologic" fetal bradycardia previously described.<sup>7-9</sup>

#### Patients and procedures

The three records discussed in this report were selected from fetal heart rate recordings where maternal hypotension was associated with conduction anesthesia and were made with electronic techniques previously described<sup>10, 11</sup>; they are graphs of the instantaneous rather than the average fetal heart rate. Each has been selected to demonstrate a particular point and is generally typical of the remainder of the group (total 12) where maternal hypotension was noted. Momentary interruptions of the record are shown as blank spaces.

Uterine contractions were determined by palpation of the abdomen and correlation with changes in the base line of the fetal ECG that accompany uterine activity. Blood pressure was determined by careful auscultation by a single observer at frequent intervals, and the infant was scored according to the Apgar scoring method.<sup>12</sup>

#### Results

Fig. 1 is the fetal heart rate pattern of a 35-year-old gravida vi, para v, term patient with the cervix at 5 cm. dilatation and the vertex at 0 station. Her blood pressure on admission was 110/70. A short time before

the beginning of the record shown in Fig. 1, the patient had received lumbar peridural anesthesia. The blood pressure was stable at 118/60. Three minutes after the reading of 118/60 recorded on the lower portion of the graph, the blood pressure fell to 80/55 and hypotension continued for about 7 minutes. About 5 minutes after the onset of known hypotension, the fetal heart rate slowed from 130 beats per minute to 70 to 80 beats per minute and then slowly returned to normal 5 minutes after the systolic blood pressure returned to 100 mm. Hg. Note the delay in the onset of fetal bradycardia following maternal hypotension and a similar delay in return to normal after normal blood pressure is again established.

A mild fetal cardiac irregularity is associated with the bradycardia. One hundred per cent oxygen was administered to the mother during the interval shown. Its role in restoring the fetal heart rate to normal is not clear since the patient had a normal blood pressure at least one minute before the oxygen was started. The infant at delivery was in good condition (scored Apgar 8).

Fig. 2 is a fetal heart rate recording made from a 21-year-old gravida ii, para i, Negro woman at 38 weeks of gestation at the time of repeat cesarean section. The patient had received lumbar peridural anesthesia. This portion of the record was made while the abdominal and intrauterine incisions were being carried out and shows a bradycardia pattern similar to that in Fig. 1. In this instance, the maternal blood pressure was checked more frequently after fetal bradycardia was noted. A vasopressor was administered and the blood pressure rose almost immediately, but 6 minutes elapsed before the fetal heart rate returned to almost normal levels. The remainder of the recording was disrupted by delivery. The baby was in good condition at birth.

The fetal heart rate patterns associated with frequent, strong uterine contractions and concomitant hypotension are shown in Fig. 3, 4. The patient was a 24-year-old gravida i, para 0, at 40 weeks of gestation

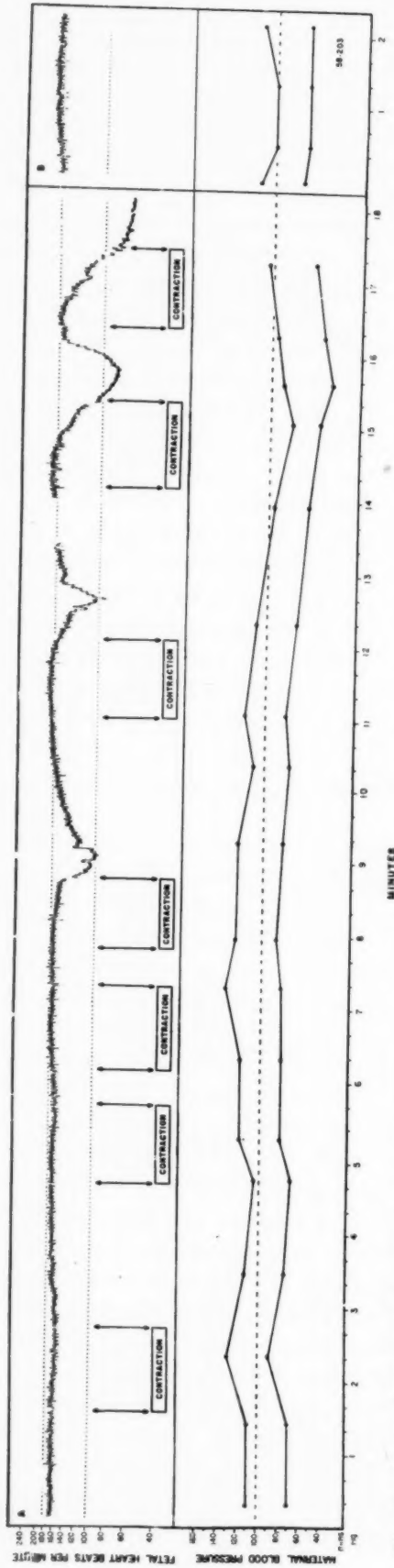


Fig. 3. *A*, Fetal bradycardia associated with strong and frequent uterine contractions in late labor in a hypotensive patient. Note tachycardia preceding bradycardia. *B*, Fetal tachycardia recorded 6 minutes after the episode of bradycardia shown in *A*.

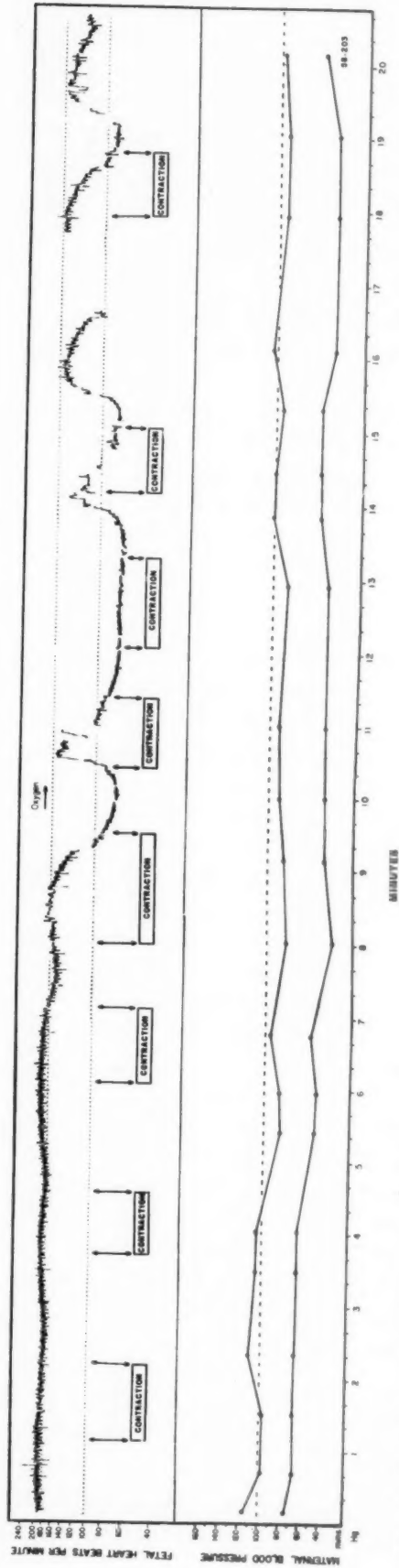


Fig. 4. Profound and prolonged fetal bradycardia associated with frequent and strong uterine contractions and concomitant maternal hypotension. Note the onset of bradycardia toward the end of the third and fourth contractions. Oxygen was administered as indicated by the horizontal arrow and was continued until delivery.

whose blood pressure on admission was 130/66. Thirteen minutes before the start of the record of Fig. 3, *A*, the patient had received low spinal anesthesia, and the blood pressure had remained relatively stable. The blood pressures determined during the period of this tracing are shown in the lower portion of the graph. The patient had a "rim of cervix" and the vertex was at 0 station. Four contractions, each lasting about one minute and recurring every 2 minutes, preceded the first contraction shown in Fig. 3, *A*. In less than 2 minutes, a group of 3 strong, closely-spaced contractions occurred, the last of which was associated with fetal bradycardia which became progressively worse. This is probably due to the frequent, strong contractions and additional insult resulting from the concomitant maternal hypotension which later developed and is shown in the later portion of the tracing. Note the mild tachycardia preceding the bradycardia. Six minutes of the record immediately following the end of this tracing (Fig. 3, *A*) was lost because of difficulties with the recording apparatus; however, a short section of the record (Fig. 3, *B*) obtained immediately after repair of the apparatus shows fetal tachycardia also.

Fig. 4 is a continuation of the record of Fig. 3, *B*. (Fig. 3, *B* has been taken from the early portion of this record.) It shows another prolonged episode of maternal hypotension during which the patient had very frequent and strong contractions. The profound and prolonged bradycardia is seen readily. Note the onset of bradycardia toward the end of the third contraction and again toward the end of the fourth contraction. (This late onset appears to be of value in differentiating "hypoxic" from "cord compression" types of bradycardia.<sup>7</sup>) With the return of maternal normotension and the administration of oxygen (begins at arrow and given until delivery) there was a gradual relief of the bradycardia. Forceps were applied shortly after the end of the record shown in Fig. 4. The baby was scored Apgar 5 at one minute. Fresh meconium

was appearing at the anal opening, but the amniotic fluid was clear.

### Comments

The fetal bradycardia patterns associated with maternal hypotension appear to be primarily "hypoxic" in type and differ from those noted with umbilical cord compression where vascular reflexes and changes in fetal hemodynamics may produce bradycardia not necessarily related to hypoxic fetal myocardial depression.<sup>7</sup> While it is not possible with present techniques of studying the human fetus to determine the mechanism underlying the bradycardia associated with umbilical cord compression, studies of these phenomena in fetal lambs suggest the plausibility of the above explanation.<sup>13</sup>

The few minutes' delay in the onset of fetal bradycardia following maternal hypotension and a similar delay in return to normal following re-establishment of normotension also suggest a gradual process. Dawes<sup>14</sup> has shown that if ewes are given low concentrations of oxygen in inspired air, the oxygen saturation of both the maternal and fetal blood falls, but the fetal lags a few minutes behind the maternal. The delayed fetal bradycardia associated with maternal hypotension may have a similar basis. The mild fetal tachycardia before the bradycardia shown in Fig. 3, *A* suggests a gradually increasing hypoxia to which the first response is tachycardia. As the anoxia becomes more severe, bradycardia develops. The probability that this bradycardia is "hypoxic" in etiology is also suggested by the tachycardia (Fig. 3, *B*) following it. While tachycardia is usually present following prolonged "hypoxic" bradycardia associated with hypotension, abnormal uterine tone, and frequent strong uterine contractions, it is not always evident before the onset of "hypoxic" bradycardia (Fig. 1 shows no tachycardia before the bradycardia while Fig. 3, *A* does). If the fetal heart rate is already rapid, no additional rise is seen before the bradycardia (Fig. 2).

Reynolds and Paul<sup>15</sup> lowered the oxygen concentration in the inspired air of ewes

and found that fetal lambs of mothers subjected to mild anoxia usually responded with tachycardia. However, there were some instances of bradycardia, as well as cases where there was no perceptible change in the fetal heart rate.

Since the majority of the hypotensive patients studied by us had received conduction anesthesia, the possibility exists that the fetal bradycardia may have been due to placental transfer of the anesthetic agent. This seems unlikely since similar bradycardia has been observed in maternal syncope unassociated with anesthesia.<sup>7</sup>

The role of maternal arterial blood pressure in maintaining intervillous space blood flow (and hence adequate fetal oxygenation) has not been fully clarified, but there is an increasing body of evidence suggesting that it is of paramount importance.<sup>1, 3-6</sup>

From the clinical standpoint, constant checking of the maternal blood pressure and the prompt correction of hypotension seem mandatory if the fetus is to have the best chance of surviving labor and delivery with an intact nervous system. This is particularly true if the mother has received conduction anesthesia and labor is being stimulated with an oxytocic.

The limited number of patients who have been studied continuously during labor does not permit an accurate assessment of the effect on fetal bradycardia of giving 100 per cent oxygen to the hypotensive mother. This should be quite important, but in practice it seems to have less effect on the fetal bradycardia than raising the maternal blood pressure.

The long-recognized association of fetal bradycardia and maternal hypotension has

been confirmed by these studies. This is particularly true of the delay in the onset of bradycardia so carefully defined by Hingson and Hellman.<sup>1</sup> Some additional information may be gained from the knowledge that this type of bradycardia appears to be "hypoxic" and is different from that noted with umbilical cord compression. Its real significance, however, must await accurate measurement of uterine artery  $pO_2$ , simultaneously correlated with similar studies of the intervillous space, and amniotic fluid and intramyometrial pressures. The measurements thus obtained would aid in the assessment of the fetal heart rate patterns. The total data should then be considered in the light of the later mental and physical performance of the infant.

#### Summary and conclusions

1. Maternal hypotension of less than 100 mm. Hg systolic pressure may be associated with "pathologic" fetal bradycardia of a "hypoxic" type. The bradycardia begins within a few minutes after the onset of maternal hypotension and may be preceded by mild fetal tachycardia.

2. With the restoration of maternal hypotension, the fetal heart rate returns to normal after a similar delay and is usually followed by mild fetal tachycardia.

3. Maternal hypotension should be corrected promptly with vasopressor drugs. High concentrations of oxygen also should be given to the mother.

4. The need for careful observation of maternal blood pressure is emphasized. This is especially true if the uterus is being stimulated with oxytocic drugs in a patient who has received conduction anesthesia.

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# The problem of postmaturity

## A statistical analysis

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ONE unresolved problem of postmaturity is that of the apparent increase in perinatal mortality compared to term deliveries. Such authors as Clayton,<sup>1</sup> Rathbun,<sup>2</sup> McKiddie,<sup>3</sup> Walker,<sup>4</sup> Gibson,<sup>5</sup> and Higgins<sup>6</sup> have reported stillbirth rates two to three times higher in comparison to babies delivered at term. This increased risk is challenged by such authors as Daichman and Gold,<sup>7</sup> Hill,<sup>8</sup> Wrigley,<sup>9</sup> Calkins,<sup>10</sup> and Holmes,<sup>11</sup> who in the cases they examined could find no difference in the mortality rates. Holmes concluded by suggesting that postmaturity is "a state of mind of the obstetrician," and Leaman<sup>12</sup> as long ago as 1892, in cautioning against too many inductions, remarked that nature does not work in molds but by variation, and where she makes no exact limitations we should hesitate.

Speculation on the reasons for this increased risk to the fetus early focused attention on giant babies, uterine dysfunction, and senility of the placenta. These abnormal conditions tended to expose the mother to such hazards as difficult delivery, long labor, and deficiency in oxygen supply which very often proved fatal to the fetus under the strain of dystocia, toxemias, and other abnormal conditions. The actual significance, however, of some of these factors is debatable.

Recent birth weight studies in relation to the period of gestation have cast doubt on

the hazard of oversized babies in prolonged pregnancies. Calkins, Daichman and Gold, and Karn and Penrose<sup>13</sup> have demonstrated that actually between 280 and 294 days there is a leveling off of growth of the fetus with a straight line curve thereafter. The search for some indications of placental senility has proved disappointing as measured by increased fibrosis of the vessels, increased calcium deposits, or other histological change. The published reports have proved contradictory. Physiological studies on fetal oxygenation, however, have implicated the placenta indirectly. The progressive diminution in oxygen supply in the umbilical vein after 41 weeks, as demonstrated by Walker and Turnbull,<sup>14</sup> results, they believe, from placental deficiency in this postmature group. It is Walker's belief that the anoxia resulting from this reduction is responsible for the threefold increase in unexplained deaths in comparison to the anoxic deaths at term. More fortunate are the postmature babies who signal their distress by a slowing fetal heart and are delivered by a timely cesarean section. Clifford<sup>15</sup> also states that at the Boston Lying-in Hospital in recent years "probably many a baby has been snatched from the brink of disaster" by timely interference in unduly long labors complicated by fetal distress, who formerly might have died. He reports that for the years 1942-1953, 75 per cent of the postmature stillbirths occurred before 1948.

The brunt of this increased incidence of fetal distress in the postmature is apparently borne by the primigravida. In a series of

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3,504 primigravidas at Aberdeen, Walker<sup>4</sup> found in those cases of difficult labor in the primigravida at 40 weeks a fetal distress rate of 13 per cent and at 44 weeks one of 39.4 per cent. For the whole group of 3,504, he found a fetal distress rate of 8.4 per cent at 40 weeks and 25.9 per cent at 44 weeks. Clayton<sup>1</sup> found a fetal distress rate in the primigravida at 40 weeks of 5.6 per cent and in the multipara 1.3 per cent. In the postmature series, he found rates of 12 per cent and 2.7 per cent, respectively. Fitzgerald and McFarlane<sup>16</sup> found for all primigravidas a rate of 8.9 per cent and for all multiparas 4.6 per cent—but for the primigravida with prolonged pregnancy 13.4 per cent.

It is the purpose of this paper to try to resolve some of the many differences in our present concept of postmaturity, first, by statistical examination to discover if there is any real entity of postmaturity which behaves in unique and predictable manner, i.e., whether a postmature gestation is different from a normal one; second, if there is such an entity, to determine by statistical methods the specific items of differentiation between postmature and normal gestation; and, third to determine the possible method of treating or preventing complications, if any, arising from postmaturity.

#### Methods and materials

For our series, consecutive deliveries at the Sloane Hospital from 1953 to 1955 were examined excluding twins, breech deliveries, multiple births, and all deliveries before 28 weeks. Also excluded from the series were cases of uncertain menstrual dates. This group constituted 900 cases or about 12 per cent of the cases examined. Deliveries en route to the hospital were also excluded. Only those birth records were included for which complete maternal histories were available. All viable births in the hospital discharge books were used with the above exceptions. Early 1956 discharges (late 1955 deliveries) were not included. After these were subtracted from the total number re-

viewed there were left for analysis 6,235 cases.

These records were examined for duration of pregnancy, race, age, parity, menstrual history, character and duration of labor, weight of baby, fetal distress, and fetal loss.

In the many studies reported, there is some slight variation as to the duration of pregnancy beyond which it becomes "prolonged." Many have designated those cases which have gone beyond 294 days<sup>16-19</sup>; some have used a lower limit of 287 days,<sup>20, 21</sup> while a few have sampled those cases going beyond 301 days.<sup>15, 24</sup> Knowing that in any normal distribution curve of population, two standard deviations from the mean will include approximately 95 per cent of the population,<sup>22, 23</sup> we originally postulated that those cases in our study which exceeded this value would be considered postmature and would be evaluated for points of differentiation from the cases of delivery at term.

The mean duration of pregnancy in our series was 39.5 weeks, or 276.5 days. One standard deviation was computed to be 16.1 days, and two standard deviations to be 32.2 days. This is 308.7 days from the mean duration of pregnancy of 276.5 days. In the series there were found only 132 cases, or 2.1 per cent (too few for statistical analysis), which extended beyond the 308.7 days (Fig. 1).

Therefore, in order to choose a gestation time (1) which we believe might be more indicative of prolonged pregnancy because it extends further beyond the lower limit of 294 days which most authors have used; (2) which would give us a larger number of cases to work with statistically than the arbitrary two standard deviations; and (3) which would follow a suggestion of Eastman,<sup>24</sup> we have used 301 days and beyond as the lower limits of gestation for prolonged pregnancy. This included 274 patients, or 4.4 per cent of the total series.

We have compared the whole population series with the postmature population in each of the categories in which there could be a difference (e.g., age, fetal weight, fetal distress, etc.) and have examined these figures for statistical significance. In most

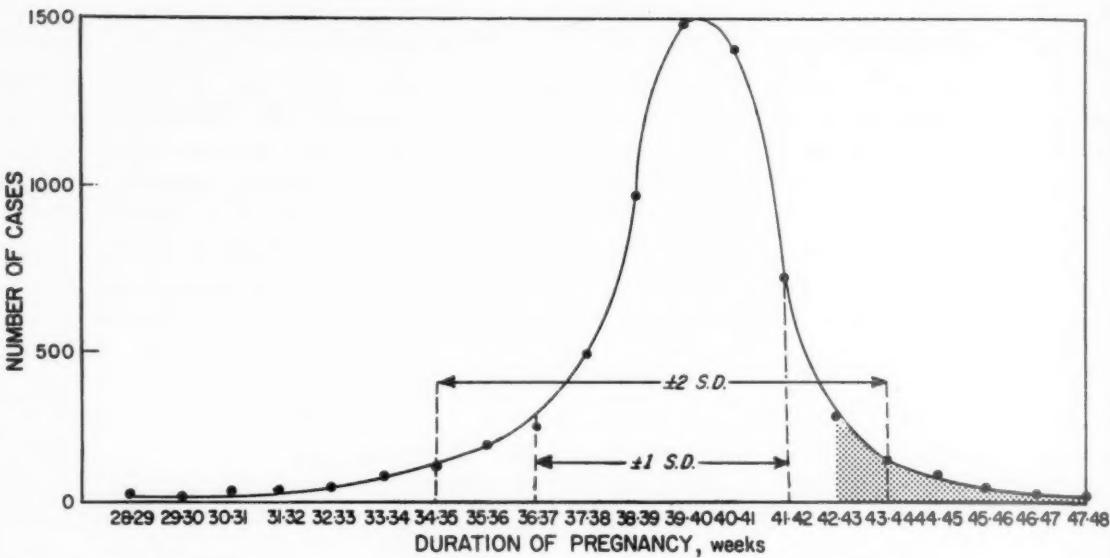


Fig. 1. Termination of pregnancy by week of gestation. Mean duration 39.5 weeks or 276.5 days. Shaded area includes cases of prolonged pregnancy studies. One standard deviation comprises normal group.

of the categories, we have also compared the postmature series with the population range which falls within one standard deviation of the mean gestation time. We believe that this will afford a comparison with a more "normal" group because in it (the range is from 37 to 42 weeks, inclusive) the obvious cases of prematurity have practically all been eliminated.

In respect to the data on fetal distress, this diagnosis is made and recorded on the clinical record if any one of the following has occurred during labor: (1) a fetal heart rate of 110 or below; (2) a fetal heart rate above 180; (3) an irregularity in the rate of the fetal heart; and (4) the presence of meconium. The fetal heartbeats are counted between contractions, and, of course, meconium may be present with or without a change in the fetal heart rate.

Results

**Race, age, and parity.** The three groups were analyzed for any differential in race, age, and parity, and no significant difference was found. The mean age for all was about 26.5 years. The incidence of primigravida is relatively the same in all groups, and the incidence of white and Negro showed

no difference in any of the groups considered (Tables I, II, and III).

**Fetal weight.** The mean weight of the overdue babies was found to be somewhat higher than that of the mature group. The mean weight of this latter group was 3,240 grams compared to a mean weight of 3,412 grams in prolonged pregnancy. This is greater by 172 grams and is held to be statistically significant (Fig. 2).

**Fetal distress.** The most striking differences between postmature patients and

Table I. Percentage representation by race and maturity

	Whole group	%	Ma-ture	%	Post-mature	%
White	3,679	59.0	2,981	59.6	176	64
Negro	2,535	40.7	2,010	40.0	98	36
Other	21	0.3	21	0.4	0	0
Total	6,235	100.0	5,012	100.0	274	100

Table II. Our series (in years)

	Whole group	Post-mature group	Fetal distress group
Mean age (years)	26.8	26.5	26.9
One standard deviation (years)	5.9	5.9	6.1



Table III. Parity by percentage distribution

	Whole group (%)	Postmature (%)
Primigravida	36.3	39.8
Para i	32.3	29.6
Para ii	17.3	17.1
Para iii	8.1	5.5
Para iv	3.2	4.4
Para v	1.6	3.3
Para vi	0.6	0.3
Above para vi	0.6	0.0

those delivered at term was found in the increased incidence of fetal distress in the former. The over-all incidence in the three groups was found to be: (a) whole group 1,252/6,235, or 20.1 per cent; (b) mature group 904/5,012, or 18 per cent; (c) prolonged pregnancy 89/274, or 32.4 per cent. This is statistically highly significant (Fig. 3).

It is commonly contended that prolonged pregnancy carries with it a greater risk to the

primigravida as manifested by the development of fetal distress. Analysis of our data showed, however, that this was true of the multigravida also (Table IV). The increase in fetal distress in prolonged pregnancy in the primigravida was  $\frac{(40.4 - 24.9)}{24.9}$ , or 162 per cent. This increase in the multigravida was found to be  $\frac{(27.2 - 14.3)}{14.3}$ , or 190 per cent. It would appear that parity per se is not the deciding factor, but that prolonged pregnancy itself increases the incidence in both primigravidas and multigravidas.

In this group of patients with prolonged pregnancy, a comparison of the weights of the babies in cases of fetal distress and in cases of normal labor showed somewhat larger babies in the former. There was a difference in the means of 164 grams. This is a significant difference, and we find that increased weight parallels increased incidence of fetal distress in the postmature but

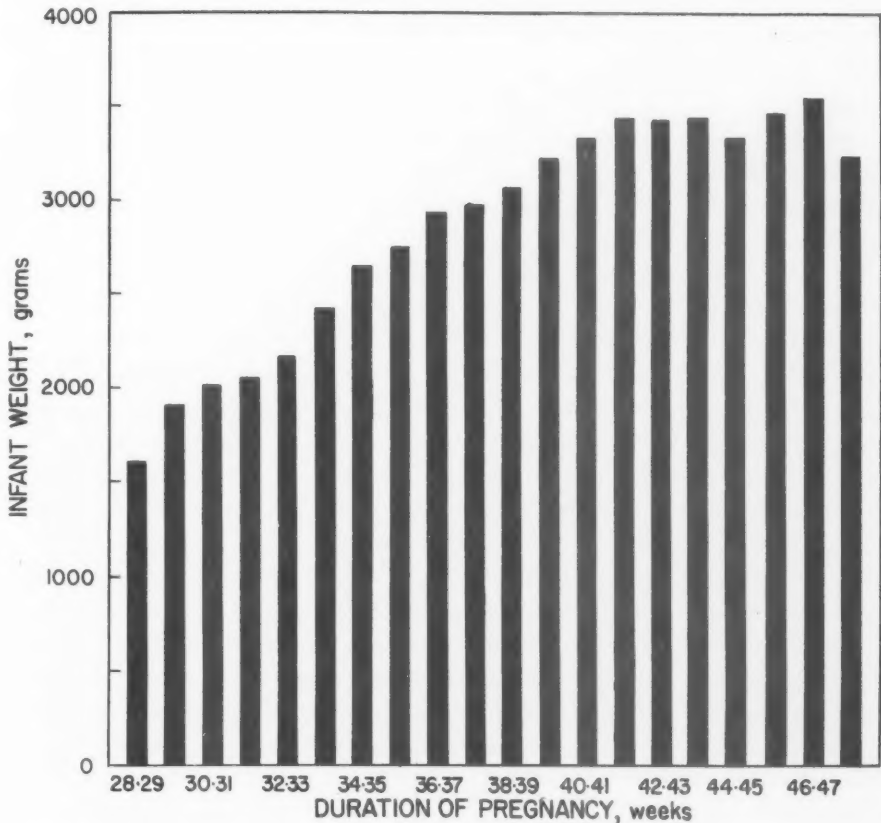


Fig. 2. Mean weight of fetus by week of gestation at termination of pregnancy.

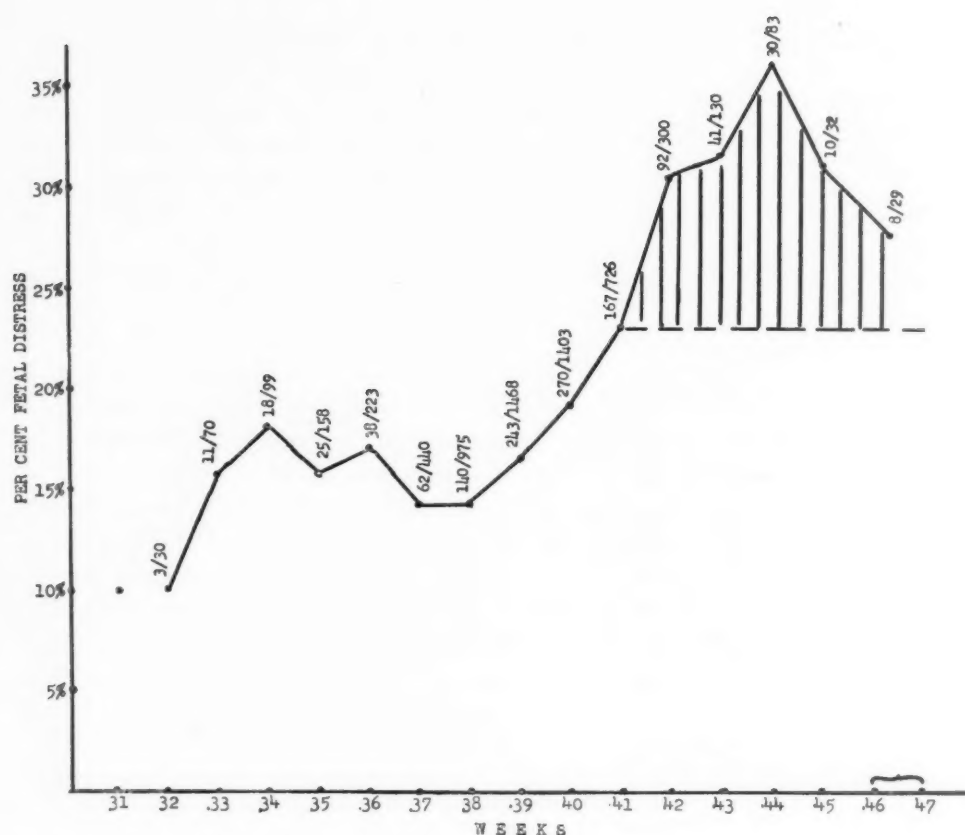


Fig. 3. Incidence of fetal distress by week of gestation.

not in the mature (Table V). We have not in this series been able to analyze the factor of pelvic disproportion and fetal distress in the heavier babies, but it does suggest a possible connection.

**Maternal age and fetal distress.** There seems to be a prevailing opinion among authors that the fetal outlook is somewhat worse with advancing maternal age in prolonged pregnancy. Since one of the warning signs might be the exhibition of fetal distress during labor, we explored those two factors. At age 40 and above in the total series there were 139 such patients. Out of these, 30, or 21.6 per cent, had labors in which distress was recorded; this was about the same as for the entire group. In the postmature group there were 89 cases of fetal distress and only one patient was found to be 40 or over. Furthermore, it is contended that labor is more hazardous for the elderly primigravida if the pregnancy is prolonged. In the entire group there were 96 elderly

primigravidas (arbitrarily so designated after 35 years of age). Fetal distress developed in 31 of these cases (32.3 per cent). In the postmature group there were 27 such patients, with only 2 cases of fetal distress, an incidence of 7.4 per cent (Tables V and VI). The oft-repeated warning concerning the elderly primigravida who is postmature was not applicable to our series.

**Fetal loss.** Examination of the fetal losses in our series showed no significant increase in prolonged pregnancy. There were 4 fetal deaths in the 274 patients (Table VII). One death occurred intrapartum, and 3 neonatally. The average weight of the babies was 3,744 grams; all exhibited fetal distress. The average length of labor was 13.5 hours, and all mothers were multigravidas.

**Fetal loss and fetal distress.** There is a direct relationship between fetal distress and fetal loss generally. There were, in the entire series of 6,235 cases, 105 deaths. Thirty-four of these were antepartum deaths occur-

Table IV. Fetal distress by parity

	Primigravidas		Multiparas		Total No.	Total series (%)
	No.	%	No.	%		
Whole group—total	2,262	36.3	3,973	63.7	6,235	100.0
Incidence of fetal distress	591	26.1	661	15.4	1,252	20.1
Mature group—total	1,776	35.4	3,236	64.6	5,012	80.4
Incidence of fetal distress	443	24.9	461	14.3	904	18.0
Postmature—total	109	39.8	165	60.2	274	4.4
Incidence of fetal distress	44	40.4	45	27.2	89	32.2

Table V. Fetal distress and weight

	Mature	Post- mature
Number in whole group	5,012	274
Mean weight of group (grams)	3,240	3,412
One standard deviation in weight of group (grams)	125	73.4
Number of fetal distress	904	89
Mean weight of fetal distress group (grams)	3,253	3,576
One standard deviation in weight of fetal distress group (grams)	121.4	152
Difference of means (grams)	13	164

ring before labor, leaving a remainder of 71. In these 71 infants, there were 39 cases of fetal distress during labor, an incidence of 55 per cent. Of the 6,130 cases terminated in a nonfatal outcome, 1,163 (19 per cent) were associated with fetal distress. To avoid the factor of prematurity, we considered for comparison only the mature and postmature groups. In the former there were 904 cases of fetal distress with a perinatal mortality of 15 and a death rate of 1.6 per cent. In the patients with prolonged pregnancy, there were 89 cases of fetal distress with 4 deaths, a rate of 4.5 per cent. This is of borderline significance ( $P = .05$ ) and indicates that fetal distress in the postmature group has a higher associated fetal loss than it does when seen in the normal group.

**Difference in type of labor and delivery.** In the term group, 91 per cent of the deliveries were spontaneous. The mean deviation of labor was 9.2 hours with a standard deviation of 5.9 hours. In the postmature

group 87.2 per cent of the patients were delivered spontaneously with a mean deviation of labor of 10 hours and a standard deviation of 6.25 hours. This is not a significant difference.

There were very few inductions of labor (in the mature group 93 out of 5,012 cases, and in the postmature group 9 out of 274). In all of these cases the pregnancy was terminated spontaneously with a mean duration of labor of 5.7 and 5.1 hours, respectively. The induction of labor was carried out by amniotomy and/or Pitocin drip, usually both.

There was only one elective cesarean section in the postmature group. Many more sections were done after the onset of labor, however, than in the mature group. Twenty-five labors, or 9.1 per cent, were terminated in this manner compared to 3.2 per cent

Table VI. Fetal distress and age

	Total No. of primi- gravidas	Total primi- gravidas with fetal distress	Primigravidas over 35 with fetal distress	
			No.	%
Whole group	2,262	591	31	5.2
Mature group	1,776	443	22	5.0
Postmature	109	44	2	4.4

Table VII. Table of fetal loss

	Number	Deaths	Per cent fetal loss
Whole group	6,235	105	1.68
Mature group	5,012	47	0.95
Postmature	274	4	1.4

Table VIII. Types of labor and delivery by weeks

Type of labor and delivery	Weeks					
	37-39	39-41	41-43	43-45	45-47	47
Spontaneous	1,178 (83.2)*	2,693 (93.8)	956 (93.2)	188 (88.2)	42 (85.7)	9 (75 )
Induced	35 ( 2.5)	49 ( 1.7)	15 ( 1.5)	6 ( 2.8)	2 ( 4.1)	1 ( 8.34)
Cesarean section after onset of labor	63 ( 4.5)	93 ( 3.2)	51 ( 5.0)	18 ( 8.5)	5 (10.2)	2 (16.6 )
Elective cesarean section	139 ( 9.8)	36 ( 1.3)	4 ( 0.4)	1 ( 0.5)	0	0
Total	1,415	2,871	1,026	213	49	12

\*Numbers in parentheses are percentages.

in the term group. There were 16 cases of fetal distress in these 25 patients, a rate of 64 per cent. Twenty patients were primigravidas, 11 of whom showed fetal distress, a rate of 55 per cent. The 5 multigravidas who had cesarean sections all showed fetal distress. The weight of the baby was not greater than in the noncesarean group. The average maternal age was 26.2 years. The average duration of labor before cesarean section was performed was 16.3 hours (Table VIII).

Summary

An analysis of 6,235 consecutive deliveries showed that 274 or 4.4 per cent were prolonged beyond 301 days. Comparison of these 274 patients with the group delivering at term showed: (1) there was no difference in age, race, or parity; (2) no special risks were encountered by the patient of advanced age or by the elderly primigravida; (3) there was no increase in perinatal mortality in the postmature patients; (4) the duration of labor and the number of spontaneous deliveries was about the same; (5) there was, however, a small but significant increase in weight of the overdue baby; (6) there was quite a significant increase in fetal distress, both in the multigravida and

in the primigravida; and (7) there was a threefold increase in cesarean sections after the onset of labor in prolonged pregnancy.

Conclusion

Although we did not find an increased loss in prolonged pregnancy, we have interpreted the increased resort to cesarean section during labor as a possible reason for the reduction in perinatal mortality. Even with the high incidence of recorded fetal distress, a large majority of patients were delivered normally. The increased reliance on cesarean section in this group suggests, however, that a more serious degree of unexplained distress was encountered, whatever might have been the cause, or that too many cesarean sections were done in undue alarm. We feel justified in concluding that unexplained fetal distress is more common than at term and that the expeditious termination of labor by cesarean section will have to be carried out in some cases in order to effect the delivery of a living child.

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# Cesarean section for fetal distress

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DURING the past decade there has been an increasing tendency to regard fetal distress as an indication for cesarean section. This attitude stems from the greater emphasis now placed on fetal salvage as well as from the greatly increased safety of the operation for the mother.<sup>1-5</sup>

The perinatal mortality figure at the Mount Sinai Hospital excluding babies weighing under 1,000 grams is 21.4 per 1,000 births (Table I). Of the 459 deaths comprising this group, 93 were caused by anoxia or trauma, and it is evident that aside from the prevention of premature birth the most likely area for improvement in fetal salvage lies in this class.

Hence, a study of fetal distress has been undertaken to determine the value of cesarean section in lowering the perinatal mortality caused by fetal anoxia. This was done by comparing the results of cases of fetal distress where delivery was by cesarean section with the mortality in cases of fetal distress in which cesarean section was not done. We also sought to determine what factor should dictate the choice of abdominal or vaginal delivery.

The objection has frequently been raised that the performance of cesarean section for fetal distress can easily lend itself to abuse. It is important, therefore, to establish the criteria of fetal distress and assess their gravity. The fetus ordinarily signals its distress by changes in the physiological activity of the bowel and the heart. Anoxia of the fetal gut causes a relaxation of the

anal sphincter and heightened peristalsis; in a vertex presentation the passage of meconium is indicative of compromise to the fetal circulation. But this sign is masked if the membranes are intact, or, having ruptured, if the vertex is sufficiently applied to the cervix to prevent escape of amniotic fluid.

Von Winkel,<sup>6</sup> in 1903, was the first to postulate that a fetal heart rate over 160 or below 100 beats per minute was presumptive evidence of distress. Lund,<sup>7</sup> however, believed that tachycardia is not as important as bradycardia. In a series of 250 cases, he found a transient tachycardia during labor in 17.6 per cent, and persistent tachycardia in 5.6 per cent without any correlation with fetal distress. Fitzgerald and McFarlane<sup>8</sup> reviewed this subject in 1955 and were struck by the scarcity and vagueness of its mention. They emphasized the significance of bradycardia, arrhythmia, and the expulsion of frank meconium. Steer<sup>9</sup> analyzed a series of 1,215 cases of

Table I. Perinatal mortality (1953-1957)

	Still- births	Neonatal deaths	Total
Malformation	25	32	57
Deaths before admission	161	0	161
Diseases of the newborn	0	59	59
Prematurity and prematurity with disease	23	66	89
Other causes (anoxia, trauma, etc.)	48	45	93
Total	257	202	459

From the Obstetrical Service of Dr. A. F. Guttmacher, the Mount Sinai Hospital

fetal distress at the Sloane Hospital for Women in New York with respect to the importance of the various signs of fetal distress and found that each category carried an appreciable risk. He stated that a fetal heart rate over 180 was the most dangerous category, with an associated fetal mortality of 7.7 per cent. The least dangerous was the appearance of meconium in a vertex presentation without change in fetal heart rate or rhythm, and carrying with it a 4.5 per cent mortality.

British obstetricians are utilizing cesarean section in the treatment of fetal distress more frequently than heretofore. For example, Dumoulin and Martin<sup>10</sup> in 1957 reported a series of 130 consecutive cases of cesarean section performed because of fetal distress, excluding those associated with placental separation and prolapse of the cord. They stated that fetal distress of sufficient severity to require cesarean section occurred in about 1 per cent of their patients, and that the problem was especially serious in the postmature primipara. Fitzgerald and McFarlane<sup>8</sup> analyzed a group of 206 cases of fetal distress from the Ashton General Hospital and concluded that a policy of active intervention as soon as fetal distress was recognized lowered the stillbirth percentage from 25 to 13. Walker<sup>11</sup> studied the problem in Aberdeen and made a strong plea for the greater use of cesarean section for fetal distress in elderly primiparas unless delivery was relatively imminent. Louw<sup>12</sup> of South Africa stated flatly that fetal distress is a most unsatisfactory indication for cesarean section, but later in the same discussion he conceded that the combination of fetal distress and postmaturity offers a valid indication for the operation.

In America, probably the prevailing opinion is typified by an editorial comment appearing in the *Obstetrical and Gynecological Survey* in 1955<sup>13</sup>: "In the absence of prolapse of the umbilical cord operative interference for fetal distress has not been generally accepted because fetal heart alterations may be transitory and because

there is often reason to believe in such cases that the baby is already damaged."

Halsey and Douglas<sup>14</sup> in their recent study from the New York Hospital present a different viewpoint. In a 10 year period from 1945 through 1954, they reported 125 cesarean sections for fetal distress, most of them in the second 5 year period. During the years 1945 to 1949 the number of fetal deaths during labor among infants over 2,500 grams or 36 weeks' gestation was 10.9 per cent of the total perinatal loss, but in the subsequent period, 1950 to 1954, this was reduced to 4.9 per cent, and they concluded that the management of fetal distress during labor by cesarean section has been an important factor in the marked decrease in fetal deaths during labor at the New York Lying-In Hospital in recent years.

#### Material

We are reporting a series of 55 consecutive cesarean sections performed for the primary indication of fetal distress, excluding cases in which the operation was necessitated by abruptio placentae, prolapse of the umbilical cord, or placenta previa. The incidence of cesarean section for the 5 year period, 1953 to 1957, for both private and clinic patients is 1,250, or 5.88 per cent of the total number of deliveries. Of these, 2.79 per cent were primary and 3.09 per cent were repeat sections. The 55 cesarean sections performed because of fetal distress, therefore, represent 9.2 per cent of the primary sections and 4.4 per cent of the total number of sections.

There has been widespread discussion of the importance of the patient's age, parity, and duration of pregnancy as factors affecting the occurrence of fetal hypoxia during labor. It is germane, therefore, to introduce at this point the topic of fetal oxygenation before proceeding further with a consideration of the clinical material. It is axiomatic that the fetus depends on the maternal circulation for an adequate supply of nutrients, including oxygen, to promote its growth and development. However, oxygen is unique among the other

substances in that it cannot be stored. The supply of oxygen available to the fetus changes with the progression of pregnancy.

Barcroft and Young<sup>15</sup> demonstrated in the postmature rabbit fetus that blood taken from the cranial venous sinus had oxygen saturation in the anoxemic level. Walker<sup>11</sup> studied the oxygen levels in the blood of the human fetus in the latter half of pregnancy and found that the oxygen content in the umbilical vein falls slowly from the 14 volumes per cent (70 per cent saturation) at the thirtieth week to 12 volumes per cent (60 per cent saturation) at the thirty-ninth to fortieth weeks. Thereafter there is a rapid fall and it may be less than 8 volumes per cent (30 per cent saturation) at the forty-third week. Walker indicates this as the "distress level" at which time there is little or no reserve of oxygen to compensate for any other factor which might interfere with the oxygen supply. If the fetus begins labor at this level it will be much more likely to show distress than the relatively well-oxygenated fetus of 40 weeks. He presented the results of 11,051 cases in which the still-birth rate was 11.7 for deliveries in the fortieth week as compared to 28.5 in the forty-third week.

Walker's hypothesis was substantiated by McKay<sup>16</sup> and Minkowski<sup>17</sup> but could not be confirmed by Bancroft-Livingston<sup>18</sup> or Rooth and Sjostedt,<sup>19</sup> and further experimental work is necessary before any accurate conclusions can be drawn.

Tables II-IV represent a summary of the relationship of age, gravidity, and duration of pregnancy in the 55 cases of cesarean

section for fetal distress, and a comparison is made with a sample of 200 patients who had normal uncomplicated labors resulting in the vaginal delivery of a live healthy infant. This control group was selected in the same proportion of private to clinic patients as in the cesarean group.

From an examination of these figures several significant facts are apparent:

1. In the fetal distress cesarean group the ratio of primiparas to multiparas is 4:1. In the control group it is 1:10.

2. In the fetal distress cesarean group the percentage of primiparas who are 30 years or older is 27.3 per cent. In the control group it is 2.5 per cent.

3. In the cesarean group 25 of the 55 patients (45.6 per cent) had pregnancies of 42 weeks or more, and of this number 23 (41.9 per cent) were primiparas. In the control group 5 patients of the 200 (2.5 per cent) had prolonged pregnancy and only 1 (0.5 per cent) was a primipara.

4. In the cesarean group 12 of the 25 prolonged pregnancies (21.8 per cent) occurred in patients 30 years of age or older. In the corresponding group of the control series it was only 1.5 per cent.

Among the primiparas, 37 came to section when the cervix was 6 cm. or less dilated and there was the likelihood of many hours of labor ahead (Table V). In the remaining primiparas it was believed that the gravity of fetal distress was too pronounced to permit even brief temporization. It will be noted that 2 multiparas were delivered by cesarean section at or near full dilatation. In the first instance forceps were ap-

Table II. Relationship of age and parity

Age (years)	Primiparas		Multiparas	
	Cesarean section (%)	Normal vaginal deliveries (%)	Cesarean section (%)	Normal vaginal deliveries (%)
Under 25	20.0	2.5	1.8	20.0
25-29	32.7	4.5	9.0	31.5
30-34	12.7	2.0	3.7	27.0
35 plus	14.6	0.5	5.5	12.0
Total	80.0	9.5	20.0	90.5



Table III. Relationship of duration of pregnancy and parity

Duration of pregnancy (weeks)	Primiparas		Multiparas	
	Cesarean section (%)	Normal vaginal deliveries (%)	Cesarean section (%)	Normal vaginal deliveries (%)
36-38	9.0	1.5	9.0	8.0
39-41	29.1	7.5	7.3	80.5
42	21.8	0.5		1.0
43	12.8		3.7	0.5
44 or over	7.3			0.5
Total	80.0	9.5	20.0	90.5

Table IV. Relationship of age and duration of pregnancy

Duration of pregnancy (weeks)	Under 25		25-29		30-34		35 and over	
	Cesarean section (%)	Vaginal (%)	Cesarean section (%)	Vaginal (%)	Cesarean section (%)	Vaginal (%)	Cesarean section (%)	Vaginal (%)
36-38	1.8	3.0	12.7	3.0	1.8	1.0	1.8	2.0
39-41	10.9	20.0	14.5	31.5	5.5	26.5	5.5	10.5
42	5.5		7.3	0.5	1.8	1.0	7.3	
43	1.8		5.5		3.6	0.5	5.5	
44 or over	1.8		1.8	0.5	3.6			
Total	21.8	23.0	41.8	35.5	16.3	29.0	20.1	12.5

plied at full dilatation in an attempt to convert a brow to a vertex presentation. The fetal heart dropped from 140 to 100 and then disappeared entirely for a few seconds. The patient was transferred to the operating room for immediate section and a live baby was obtained. The second case was that of a 38-year-old multipara in the forty-third week of pregnancy with severe anemia. At 7 cm. dilatation the fetal heart rate dropped from 140 to 100. Despite the administration of oxygen it further decreased to a rate of 80 to 90 and became

irregular. Although the cervix was now 9 cm. dilated, the vertex was still at minus 1 to minus 2 station, in occipitoposterior presentation, and the baby's weight was estimated at more than 4,000 grams. Further observation was abandoned, and a 4,270 gram live baby was delivered by cesarean section.

In 31 of the 55 patients the signs of fetal distress supervened within 12 hours of the onset of labor. Five patients, all primiparas, had a labor prolonged beyond 24 hours when fetal distress was noted (Table VI).

Table V

Dilatation (cm.)	Status of cervical dilatation at time of cesarean section		
	Primi-gravidas	Multiparas	Total
1-2	7	4	11
3-4	18	3	21
5-6	12	2	14
7-8	7		7
9 to full dilatation		2	2
Total	44	11	55

Table VI. Number of hours of labor when fetal distress was first noted

Duration of labor (hours)	Primi-gravidas	Multiparas	Total
Under 6	8	5	13
6-11	13	5	18
12-17	14	1	15
18-23	4		4
24 or over	5		5
Total	44	11	55

It is apparent that there is no remarkable difference in birth weight in the two groups despite the greater incidence of prolonged pregnancy among those patients delivered by cesarean section (Table VII). This would seem to bear out the observation that the baby usually gains little weight beyond the fortieth week.<sup>20, 21</sup>

Table VII. Fetal weight

Weight (grams)	Cesarean section		Control group	
	No.	%	No.	%
2,000-2,499	3	5.4	10	5.0
2,500-2,999	11	20.0	50	25.0
3,000-3,499	27	49.1	84	42.0
3,500-3,999	10	18.2	36	18.0
4,000 or over	4	7.3	20	10.0
Total	55	100.0	200	100.0

Pitocin was utilized more frequently in this group than is the general custom on the Obstetric Service (Table VIII). Five of the 9 patients in whom labor was induced had pregnancies 42 weeks or more in duration. In 6 of these inductions, it appeared on hindsight that the cervix was unfavorable and the presenting part high. In 4 cases, fetal distress developed within an hour of the induction. In 7 of the 9 inductions, dilatation did not advance beyond 4 cm. In the eighth case after 49 hours of labor the cervix was 6 cm., and in the ninth case after 23 hours the dilatation was 7 cm. when the cesarean section was done.

Table VIII. Pitocin administration

	Cesarean section for fetal distress		Total no. of deliveries (21,413)	
	No.	%	No.	%
For induction of labor	9	16.3	2,319	10.8
For stimulation of labor	12	21.8	2,018	9.4

Twelve patients had Pitocin stimulation for desultory labor, and 5 of these had a pregnancy of 42 weeks or more. In 4 cases

Table IX. Duration of symptoms of fetal distress prior to operation

Less than 1/2 hour	20
1/2-1 hour	17
1-2 hours	7
2-3 hours	4
3-4 hours	3
4-5 hours	2
5-6 hours	0
Over 6 hours	2
Total	55

distress developed within an hour of the onset of the Pitocin drip.

On the basis of 21 cases, sweeping conclusions cannot be drawn about the role that Pitocin had in the production of fetal distress. One may infer, however, that there is need for a greater degree of caution in the utilization of Pitocin in the primipara with a postmature fetus.

Obviously, the risk to the fetus bears a direct relationship to the time interval between the first notation of fetal distress and delivery. Twenty of the patients were operated upon within a half hour and another 17 between one half and one hour of its recognition (Table IX). These represent cases in which the signs of fetal distress developed suddenly, were of moderate to marked severity, did not improve with oxygen, and, hence, the pregnancy was terminated by prompt cesarean section. In the remaining 18 patients the time lag was longer either because the signs of distress were less marked or because there had been temporary improvement followed by a recrudescence. In nearly all cases there remains an unknown factor, the exact moment of the onset of distress.

In general it would seem that resuscitation time will vary directly with the severity of compromise to the fetal circulation in utero. Yet, in one case of neonatal death, the breathing and crying times were noted within one minute of delivery, and the baby died in a few hours. Postmortem examination of the baby showed massive aspiration of amniotic fluid and meconium. The cause of death was acute bronchopneumonia.

Table X. Anesthesia and resuscitation time\*

	Spinal	General
Less than 1 minute	22	10
1-3 minutes	7	4
4-6 minutes	2	5
7-9 minutes		
10 minutes or more	1	1
Total	32	20

\*There were also 3 stillborn babies.

When spinal anesthesia was used the average time that elapsed between the introduction of the Pontocaine and the skin incision was 8.4 minutes. The general anesthetic agents used were either cyclopropane or ethylene, and the average time for induction was 2.9 minutes. In all cases the operation performed was of the low flap variety, and the average time between skin incision and delivery was 8.3 minutes. A spinal anesthetic will take longer but will permit better oxygenation of the fetus, while a general anesthetic will produce rapid induction but must be followed by speedy operation.

### Results

The perinatal mortality in this series of 55 cesarean sections was 3 stillbirths and 1 neonatal death (7.3 per cent), which is almost the same as the figures of 8.8 per cent reported by Hess,<sup>1</sup> 8 per cent by McCall and Fulscher,<sup>22</sup> and 7.7 per cent by Dumoulin and Martin.<sup>10</sup> Halsey and Douglas<sup>14</sup> noted a perinatal mortality of 14.3 per cent in the years 1945 to 1949, but, in the years 1950 to 1954, a period roughly comparable to our own, they were able to reduce that figure to 6.7 per cent, giving an over-all percentage of 8.8.

A brief analysis of each fetal death follows:

The first stillbirth was in a 35-year-old primipara at term. The first indication of fetal distress was discovered 7 hours after the onset of labor when the fetal heart rate accelerated from a baseline figure of 140 to 212. Twenty minutes later an amniotomy was performed with a cervical dilatation of 3 cm., releasing me-

conium-stained fluid. Coincidentally, the fetal heart rate dropped precipitately to 100 and remained at that rate for 10 minutes before it returned to 160. The second phase of fetal distress supervened with startling suddenness 4 hours after the first warning, when the fetal heart rate dropped to 40 to 60 per minute. The cervix was now 7 cm. dilated. Abdominal delivery of a 3,210 gram infant was effected in less than 30 minutes, but the fetal circulation had been too severely compromised to permit the infant's survival. Postmortem examination revealed generalized venous congestion with massive aspiration of amniotic fluid, including meconium. Cause of death was "intrapartum asphyxia, cause not anatomically determined."

The second stillbirth occurred in a 34-year-old primipara 5 weeks beyond term with mild pre-eclampsia. Two attempts at induction of labor with Pitocin were discontinued because of fetal distress. A desultory labor ensued the following day but no significant progress was noted. On the third day an intrapartum infection developed and the fetal heart tones were noted to be of poor quality. Cesarean section under spinal anesthesia was performed and a stillborn infant weighing 2,850 grams was delivered. The placenta had multiple infarcts and focal calcific deposits. There was an acute amnionitis with umbilical vasculitis. The postmortem examination of the infant showed nothing remarkable.

This patient exemplifies the malignant triad of primiparity, advanced age, and prolonged pregnancy. A fourth unfavorable factor was superimposed pre-eclampsia. On hindsight, the ominous fetal bradycardia noted after Pitocin infusion was begun should have tipped the balance in favor of immediate cesarean section, all the more so in view of the second episode of fetal distress when the induction of labor was attempted several hours later. The lethal blow to this compromised baby was provided by the intrapartum infection.

The third stillbirth was in a 31-year-old primipara 3½ weeks beyond term. An amniotomy was performed when the cervix was 7 cm. dilated, releasing thick clumps of meconium. The fetal heart rate at this time was 120 but 70 minutes later it dropped to 80, and the heart sounds were faint and irregular in rhythm. A cesarean section performed 34 minutes later yielded a stillborn infant weighing 2,950 grams. Postmortem examination showed

meconium staining of the skin and fetal membranes. Cause of death was "intrapartum asphyxia, cause not anatomically determined."

Here again one is dealing with a primipara over 30 years of age whose pregnancy was prolonged  $3\frac{1}{2}$  weeks beyond term. In retrospect, it seems that it was unwise to allow labor to continue in this particular patient until she evinced the complete clinical picture of fetal distress, and that to postpone operation until the fetal heart rate reaches this critical level will generally result in a stillborn baby.

The fourth case was a neonatal death in a 34-year-old multipara in early labor at term. The patient had one living child and had had three full-term stillbirths. There was no evidence of toxemia or latent diabetes mellitus. A notation was made in the antepartum clinic that the patient should be allowed to go into spontaneous labor but that a cesarean section should be done without hesitation unless all conditions for vaginal delivery were favorable. On admission to the hospital the fetal heart rate was 168 but the sounds were quite distant. This was interpreted to be more a case of potential rather than actual fetal distress. A cesarean section was performed one hour later under spinal anesthesia, and a 3,400 gram infant was delivered. The amniotic sac was filled with thick meconium, and although the infant breathed spontaneously it appeared to be in poor condition, and it died several hours later. Postmortem examination showed massive aspiration of amniotic fluid, including meconium, and acute bronchopneumonia. Cause of death was "respiratory obstruction secondary to intrapartum asphyxia."

In this case the problem is different from the other three since the fetal distress was never a prominent feature. It does highlight, however, the use of cesarean section for the patient with the so-called "poor obstetrical history."

#### Comment

It has not been possible to determine the actual cause of fetal distress in all of the 55 cases in which cesarean section was done. In 17 patients, approximately one third, there were various cord complications, excluding true prolapse. Halsey and Douglas<sup>14</sup> found these to be responsible in more than half of the sections that were performed because of fetal distress.

In 4 cases the placenta showed evidence of degenerative changes such as ischemic infarcts, calcific deposits, fibrosis, and excessive deposition of placental "fibrinoid." In 3 of these 4 cases the pregnancy was prolonged to 43 weeks.

Five patients were in labor more than 24 hours before evidence of fetal distress supervened. In the absence of other demonstrable causes, prolonged labor per se can be regarded as the possible etiological factor.

In the remaining 29 patients there was no obvious cause to account for the fetal distress except that in 16 the pregnancy was 42 weeks or more in duration and, of these 16, 14 were primiparas.

The question of postmaturity and its deleterious effect on the fetus has engendered a lively controversy in the past 5 years. In general, postmaturity as an obstetric entity has received greater acceptance in Britain than elsewhere. Dumoulin and Martin,<sup>10</sup> in their series of 130 cases of cesarean section performed because of fetal distress, found that in 45 per cent the gestation period was over 290 days, and, of the 10 babies that were stillborn, 9 were included in this group. McKiddie<sup>23</sup> noted that the incidence of unexplained stillbirths was 3 per 1,000 at term but increased to 11 per 1,000 in the postmature group. Baird<sup>24</sup> felt that the hazard of postmaturity to the baby was increased greatly in the older woman, especially in the primipara. He reported that the stillbirth rate in primiparas in Aberdeen had been decreased by two thirds from 1938 to 1954, partly because of the more extensive use of cesarean section in the primiparas over 25. Gibson<sup>25</sup> analyzed 5,000 deliveries and reported a twofold increase in fetal death in the forty-second week and a threefold increase in the forty-third week. He concluded that postmaturity is responsible for a definite fetal mortality primarily from anoxia in utero during the first and second stages of labor.

Despite the evidence presented above, there has been a reluctance on the part of many American obstetricians to accept postmaturity as a true entity. Series reported



by Daichman and Gold,<sup>26</sup> Tucker and Benaron,<sup>27</sup> Kunstadter and Schnitz,<sup>28</sup> and Jacobs and Morgan<sup>29</sup> have shown no evidence that prolonged pregnancy and so-called postdate labor are any cause for alarm. On the other hand, Nesbitt,<sup>30</sup> while at the Johns Hopkins Hospital, claimed that perinatal mortality was three times greater in the postmature group and that intrapartum deaths were six times greater than in the term deliveries.

There does seem to be general agreement that though a fetus remains in utero for a varying length of time beyond the due date it will seldom show at birth the clinical signs of a truly postmature infant such as described by Clifford.<sup>31</sup>

Whether or not we use the term postmaturity, prolonged pregnancy, overterm pregnancy, or postdate labor and whether we accept or reject Walker's oxygen studies, it would seem that the preponderant evidence, including our own study, favors the view that for the primipara past the age of 30 in whom labor starts beyond the forty-second week of pregnancy, there is significantly increased risk of fetal distress. With this in mind, Walker,<sup>11</sup> among others, has championed the practice of elective induction of labor in the forty-first week. This policy, however, has met with sharp criticism. In the first place, the greatest danger to the fetus in prolonged pregnancy does not lie in death in utero before labor. Second, it is of the utmost importance that the cervix be highly favorable for induction, especially in the primipara.

Therefore, despite the uneasiness of the obstetrician faced with the pregnancy advancing beyond term and despite the entreaties of the patient, it would seem that the interest of the fetus would best be served by a policy of noninterference rather than by the use of measures that are themselves more dangerous than the postmaturity.

**Fetal distress with vaginal delivery.** During this 5 year period in which 55 cesarean sections were done because of fetal distress, there were 192 cases of fetal distress

during labor which terminated in vaginal delivery. In order to make the comparison with the group who underwent cesarean section more valid, this series also excludes cases of prolapse of the cord, abruptio placentae, and placenta previa and infants who weighed under 2,000 grams or were of less than 36 weeks' gestation.

Briefly, an analysis of these cases of fetal distress with vaginal delivery reveals the following significant differences from those delivered by cesarean section.

1. The percentage of primiparas (58.4 per cent) is lower than in the cesarean section group (80 per cent).

2. The percentage of primiparas 30 years or older (13.7 per cent) is one half that of the same category in the cesarean section group (27.3 per cent).

3. The percentage of primiparas with prolonged pregnancy (12.9 per cent) is about one third of the same category in the cesarean section group (41.9 per cent).

4. When fetal distress was first noted, 80.3 per cent of the patients had attained a cervical dilatation of 7 cm. or more. Only one fifth of this number (16.3 per cent) in the cesarean section group had attained at least 7 cm. dilatation at the time of operation.

5. The percentage of patients with Pitocin induction (3.8 per cent) was about one fifth that noted in the cesarean section group (16.3 per cent).

In this group of 192 cases of fetal distress there were 20 stillbirths and 8 neonatal deaths, giving a perinatal mortality of 14.5 per cent, or twice that noted in the cesarean section group.

The group of 20 stillbirths can be divided into 4 subgroups: (A) 2 cases of rapid, tumultuous labor; (B) 5 cases of fetal distress first noted at full dilatation with subsequent rapid delivery; (C) 8 cases in which the fetal heart sounds disappeared during the first stage of labor without prior notation of signs of fetal distress (one of these was in a 34-year-old multipara with pre-eclampsia in the forty-third week of gestation; (D) 5 cases in which ample warning

of fetal distress was provided and in which a live baby might possibly have been obtained by cesarean section.

An objection may be offered that the 8 cases in Group C should not be included since no fetal distress had been clinically demonstrated.

In the group of 8 neonatal deaths, 7 cases showed the first sign of fetal distress at full dilatation and despite a rapid delivery without undue difficulty all 7 infants died within 48 hours. In the eighth case fetal distress was initiated by hypotension in the mother as a result of caudal anesthesia at 6 cm. dilatation.

**Management of fetal distress.** The management of fetal distress should be viewed from two aspects, namely the etiological and the therapeutic. From the foregoing discussion, it is clear that the elderly primipara beyond the forty-second week of pregnancy, especially if she has had antepartum bleeding or hypertension, merits special attention when she goes into labor, with meticulous observation of the fetal heart rate and, in the presence of ruptured membranes, the character of the amniotic fluid.

When any abnormality of the fetal heartbeat is detected, particularly bradycardia or irregularity, an immediate vaginal examination is imperative. If the membranes are intact they should be ruptured and the color of the amniotic fluid noted. Thick clumps of dark meconium indicate more severe hypoxia than a light greenish-tinted fluid. The examining fingers will determine the station of the presenting part, the degree of effacement, dilatation, and softening of the cervix, and whether or not there is prolapse of the cord. Oxygen inhalation is begun at once in an effort to raise the oxygen level of the relatively unsaturated fetal blood via a higher oxygen content of the maternal blood; further sedation of the mother should be interdicted and the patient placed in the Trendelenburg position. If there has been tumultuous labor or tetanic contractions, amyl nitrite is administered, and if Pitocin infusion is being used it should be stopped. Fundal pressure will intensify the disorder

of the fetal heartbeat if there is a short cord or if it is tightly looped around the infant's neck or body.

If the fetal heart rate returns to normal with oxygen inhalation, if the patient is a multipara, if the cervix is at least 6 cm. dilated, and if the quality of the labor has been good, then the patient may be further observed and vaginal delivery anticipated.

It must be kept in mind, as Nesbitt<sup>32</sup> has pointed out, that hypoxia of the fetus in utero will cause engorgement of the cerebral vessels with increased risk of cerebral injury. Therefore, although an expeditious delivery is desired, undue haste and a traumatic delivery should be avoided.

In the case of a primipara where these favorable factors do not obtain, cesarean section must be considered. This decision will be hastened if there is an abnormal presentation or poor application of the presenting part to the cervix, if at least 6 hours more of labor is anticipated, if the bradycardia persists or recurs despite the administration of oxygen, if the meconium is thick, if there has already been a labor in excess of 18 hours, if there is a "poor obstetrical history," and, finally, if the patient is postmature and over 30 years old. In effect, the obstetrician must draw up a balance sheet of the various factors involved, both tangible and intangible, before he determines which mode of delivery to employ.

It has been previously mentioned in discussion of our perinatal mortality that in 8 patients who were delivered vaginally the fetal heartbeat disappeared suddenly during the first stage of labor. It is unlikely that the lethal factor of anoxia operated with such cataclysmic force that a normal heart rate should disappear without prior warning, and the inference is plain that, if there had been constant auscultation, signs of distress would have been noted earlier. For this reason, it is suggested that a modification of the cardiotachyscope be utilized to serve as an electronic monitor in those cases where a nurse cannot be in constant attendance, and especially when the fetus is

regarded as a likely candidate to develop signs of intrapartum anoxia.

It is further suggested that in all obstetrical departments consideration be given to the location of the operating room for immediate accessibility should cesarean section be advised as an emergency procedure. In keeping with this policy, the operating room and anesthetist should be in constant readiness both day and night, so that no delay is encountered while waiting for instruments to be sterilized or for the anesthetist to arrive from another area.

### Summary

1. A series of 55 consecutive cesarean sections has been presented in which the primary indication was fetal distress.

2. The various factors involved in these 55 cases have been tabulated, with evidence that parity, age, and duration of pregnancy are important as predisposing causes.

3. The etiology has been analyzed, and more than half of the cases remain unexplained by any obvious cause.

4. Postmaturity or prolonged pregnancy has been discussed at length, particularly as it relates to fetal hypoxia. Although true postmaturity of the fetus is rare, postmaturity as an obstetric entity must be reckoned with in any attempt to increase perinatal salvage. On the other hand, induction of labor at term to avoid postmaturity is fraught with too many fetal hazards to permit its routine use.

### Conclusion

1. Prompt recognition of fetal distress is imperative. If it is marked or if persistent early delivery is vitally important and unless conditions favorable for vaginal delivery are met, a prompt cesarean section is necessitated.

2. If cesarean section is chosen, it should be performed expeditiously and the choice of anesthesia carefully considered.

3. The perinatal salvage of infants delivered by cesarean section because of fetal distress is twice that of a similar group delivered vaginally.

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Discussion

DR. SCHUYLER G. KOHL, Brooklyn, New York. Table I shows the perinatal loss associated with the various signs of fetal distress that occurred in labor, with or without complications.

The term "with or without complications" denotes complications of pregnancy. This is an attempt to remove those complications of pregnancy which, in themselves, might be responsible for an unsuccessful outcome. Those patients with no obstetrical complications had a perinatal mortality rate of 6.4 per cent in contrast to a 9 per cent perinatal mortality rate for those infants whose mothers suffered complications of pregnancy.

May I point out the fact that in the 187 uncomplicated pregnancies with meconium alone, an 8 per cent perinatal loss was suffered.

I am curious about the 192 patients who had fetal distress and who were delivered vaginally. They might be compared with the women delivered by cesarean section rather than with the random sample of 200. I am very interested in how they compared as far as the matter of parity, age, and other factors which you detailed.

With the small numbers you have, 17.3 per cent and 14.2 per cent perinatal mortality rates, in the two groups, are not significantly different from one another.

DR. BERNARD A. G. WEISL, Brooklyn, New York. As I understand "perinatal mortality" it is an index and is composed of fetal deaths

over 28 weeks, plus infant deaths under 7 days, divided by fetal deaths over 28 weeks plus total live births, multiplied by a thousand, which gives a rate per thousand deliveries. Early in this paper, Dr. Mintz gave this figure for Mount Sinai as 21.3. Later on Dr. Mintz gave perinatal mortality as percentages. The mixture of "rate" and "per cent" makes it difficult to comprehend the figures quoted.

DR. MARTIN STONE, New York, New York. I would like to ask whether the babies saved by cesarean section turned out to be normal or do some have evidence of neurological disorders or brain damage? Usually we consider as an end point fetal death or life. However, it is becoming apparent that anoxia may have a sublethal effect on the infant leading not to death but to cerebral palsy, mental retardation, or other neurological disorders. An analysis of fetal results must, therefore, include a long-range evaluation of the infants who live.

DR. D. ANTHONY D'ESOP, New York, New York. It is difficult to evaluate the treatment of fetal distress primarily because we do not have a suitable definition of it. This is shown very clearly if one goes over the reports on fetal distress and notes its incidence in different clinics. Dr. Hellman, in the paper he gave at the American Gynecological Society meeting last year from which the Table was taken that Dr. Kohl just showed you, gave an incidence of fetal distress of 2.9 per cent. In our material, if we include all the fetal heart irregularities, the tachycardias and bradycardias,

Table I. Perinatal loss associated with signs of fetal distress in labor with or without complications\*†

	No complications			Complications		
	No	Loss	%	No	Loss	%
Meconium	187	15	8.0	154	9	5.8
Meconium plus fetal heart abnormality	27	2	7.4	27	7	26.0
Fetal heart abnormality	82	2	2.4	123	11	8.9
Total	296	19	6.4	304	27	8.9

\*Term infants alive at the onset of labor only. Breech and twins excluded.

†From Hellman, L. M., et al.: AM. J. OBST. & GYNEC. 76: 998, 1958.



and all different kinds and amounts of meconium—in other words, all the deviations from the normal in these characteristics—you come up with a figure that is close to 10 per cent. Obviously, there must be something radically different here in what we use as definitions. Further, if we make more frequent observations on these patients, as we have been doing in the study on the epidemiology of cerebral palsy where we listen to the fetal heart every 15 minutes in the first stage and following each contraction in the second stage, then the incidence of these deviations in the fetal heart rate will go up to 25 per cent. Now I am not saying that these are all cases of fetal distress, for many of the changes in rate are transitory, but I do want to point out that the incidence of fetal distress will vary considerably with the care and diligence of the observer.

Besides this matter of definition and incidence of fetal distress, I think the subject has also been confused by the fact that in clinical studies of fetal distress we include conditions such as placental complications, toxemia of pregnancy, and other maternal complications that in themselves predispose to fetal death. If we want to compare the various forms of treatment for fetal distress we should include only cases of pure fetal distress, because this is what we are really interested in. We know how to treat toxemia. We know how to treat accidental hemorrhage. At least we think we do, based on studies of these specific complications. We can look upon the management of these complications within their own framework of reference. What we would like to know is how to treat unexplained fetal distress, for which reason in the collection of material for study we should purify the sample into the cases of fetal distress that we cannot explain anterospectively when the obstetrician is faced with the need to treat a bad situation in an otherwise uncomplicated case.

DR. EDWARD G. WATERS, Jersey City, New Jersey. I am afraid I still do not know for certain what patients we benefit by doing a cesarean section. By correcting the vaginal delivery percentages and fetal salvage or loss after vaginal delivery in one table and comparing the data with those cases sectioned for fetal distress, the percentage should be the same. Eliminate the 8 babies who died before delivery and the 2 with tumultuous labor, presumably delivered before cesarean section could

be undertaken, and you will see that the percentage of fetal loss in vaginal delivery or in cesarean section is almost identical. I still don't know what the exact criteria should be any more than Dr. D'Esopo.

We have recently had 2 cases where the fetal heart had been going along all right. In one, the rate suddenly dropped to 60, came back to 80-90, and stayed at 90, and a repeat section was performed. In the second, a cesarean section was performed when the fetal heart rate was 70. Both babies exhibited no evidence of distress upon delivery and both cried spontaneously; the heart rates immediately after birth were over 130. The placenta was normal in each instance. Upon completing the operation, one wondered whether he had really "salvaged" the baby.

We have had a number of patients who were delivered vaginally before section could be done and in whom the same criteria was present, as in these cases of so-called fetal distress, and the babies were delivered in exactly the same condition. It is hard to say when we actually save these babies. How can we be sure when a baby satisfying these criteria for fetal distress is actually saved by cesarean section. In about half of these patients, a half hour elapsed between diagnosis and delivery by section. This is a pretty short span of time in which to positively establish fetal distress and also save the baby.

This leads to another point. Among the criteria for fetal distress was listed postmaturity. I think postmature babies do become distressed more easily than others, which might invite a title such as "cesarean section for the postmature fetus who is in distress."

When is a baby postmature? The gestation time selected here is 43 weeks. The old idea of ovulation timing no longer is true. Many patients ovulate at odd times of the month, some even on the first day or just before the onset of menstruation, and such variances would throw calculations off a couple of weeks. So I would think on a time basis alone maximal variations must be taken into account before the fetus is declared to be postmature.

DR. MINTZ (Closing). In answer to Dr. Kohl's question, I would like to state that in the original paper I did present the comparison of results between vaginal delivery with fetal distress and cesarean section with fetal distress. The paper read this evening was necessarily somewhat

abridged, and these figures were omitted.

In answer to Dr. Weisl's question about perinatal loss, the figure 21.3 represents a mortality of 21.3 per thousand live births.

I agree with Dr. D'Esopo that a good definition for fetal distress is necessary. I did not intend to be dogmatic about the definitive criteria of fetal distress, because they are sometimes rather evanescent, particularly the rate and rhythm of the fetal heart sounds. The one sign, of course, that offers tangible evidence of distress for all to see is the passage of frank meconium.

Dr. Waters mentioned that occasionally a fetus will exhibit the signs of marked fetal distress and yet at delivery show no evidence of having been in grave jeopardy in utero. As one possible answer to his question of why certain babies should be delivered by cesarean section and others not, he offered the associated factor of postmaturity. I agree with that and

would like to add primiparity and advanced age of the mother as other factors, and last, the duration of distress prior to delivery.

Dr. Waters also inquired about the pronounced difference in perinatal loss between those babies delivered by cesarean section for fetal distress and those delivered vaginally where fetal distress had been evident. It is true that if we omit the 8 cases of intrapartum death in the latter group, in which the fetal heart sounds disappeared, the mortality figure would be reduced from 14.5 per cent to 10.8 per cent. I would like to emphasize again, however, that these 8 cases should not be discarded. Fetal distress must have been present prior to the demise, but no one was at the bedside to discover it.

Finally, in answer to Dr. Stone's question, we have as yet no figures on any long-term follow-up of these babies.

# Fetal death before the onset of labor

An analysis of 407 cases

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DURING the decade between 1944 and 1953 at Sloane Hospital for Women, there were 34,368 babies born with weights exceeding 500 grams. One thousand and seventeen, or 3.2 per cent, of these babies died; of these, 407 died before the onset of labor. It is the purpose of this paper to present some of the more interesting data concerning these latter 407 fetal deaths.

The incidence of antepartum death of fetuses which exceeded 500 grams in weight was 1.2 per cent. The corresponding figure for fetuses exceeding 1,000 grams was 0.94 per cent, which is somewhat lower than the incidence reported by Dippel<sup>3</sup> and Tricomi and Kohl.<sup>9</sup>

## Material

Two hundred and ninety-four antepartum fetal deaths occurred among 20,578 deliveries on the ward service and 113 among 13,790 private deliveries, an incidence of 1.4 per cent and 0.8 per cent, respectively. This greater incidence of fetal deaths among ward patients, although previously reported,<sup>1, 3-6</sup> is difficult to explain precisely. The greater number of Negro patients and the higher incidence of toxemia in this group may be responsible factors.

Sixty-seven per cent of the patients in this series were white and 33 per cent Negro, as opposed to an incidence of 75 per cent white

and 25 per cent Negro on the obstetrical service as a whole during the time studied. This would indicate an increased antepartum fetal risk among Negro patients. Dippel<sup>3</sup> reported a similar finding.

One hundred and seventy-three of the patients were nulliparous and 234 were parous. This represents a ratio almost identical to that of the service as a whole.

Among the 401 patients whose ages were recorded, the average was 30.1 years; the range, 15 to 46 years. Twenty-six, or 6.4 per cent, were over 40 years of age, in contrast to 3.2 per cent among the other patients delivered during this decade. This trend of more frequent intrauterine fetal deaths among older patients has been previously observed.<sup>7, 9</sup>

Among the 234 parous patients in this series, 50, or 21 per cent, had had previous stillbirths. Forty-two had had one previous stillbirth and 8 had had two. Of these 50 patients, 19 had Rh incompatibility, 6 had anomalous progeny, and 5 were diabetic; the remaining 20 repeat stillbirths could not be related to any condition which is thought to be associated with repetitive fetal loss. The incidence of previous stillbirth was only 1.6 per cent among the patients in this series in whom the cause of the stillbirth was unknown.

Of the 407 babies in this series, maceration was present in 309, absent in 59, and unrecorded in the remainder.

## Causes of antepartum fetal death

It is axiomatic that the causes of intrauterine fetal death are varied and often ob-

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scure. Otherwise it might be a less common occurrence. Several factors may sometimes be apparent; with equal frequency, the cause is unknown.

In view of the complexity of this problem, it is surprising that the causes of fetal death in this series can be categorized rather simply in only ten groups. These groups are enumerated in Table I and discussed in the ensuing paragraphs. When more than one factor was encountered, the more lethal was considered the primary cause.

**1. Cause unknown.** Probably the most striking single feature of Table I is that there was no demonstrable cause of fetal death in 27.8 per cent of the cases—the largest single group. Stated more dramatically, during the 10 years studied there was approximately one antepartum fetal death every month which occurred in the third trimester of an ostensibly normal pregnancy and could not be explained. Not since the discovery of the Rh factor has any real progress been made in the diagnostic dissolution of this large group of enigmas.

In rather marked contrast to previous decades, no fetal deaths in this series were attributed to syphilis.

**2. Toxemia of pregnancy.** Toxemia of pregnancy and allied conditions were thought to be the direct cause of death in 106, or 26.0 per cent, of the fetuses in this series. This group includes 50 patients with

pre-eclampsia, 27 with hypertension, 14 with hypertension and superimposed pre-eclampsia, 5 with eclampsia, and one with chronic nephritis. The average duration of gestation at the time of fetal death was 34.8 weeks; the average interval between fetal death and delivery was 6.8 days.

In addition to these 106 deaths there were 20 other cases of fetal death in which toxemia was associated with abruptio placentae. These cases are considered under the group with premature separation of the placenta. Were these 20 cases added to this group, toxemia would be the etiological factor in 30.9 per cent of the series, rendering it the largest of the ten categories.

**3. Premature separation of the placenta.** The third largest group was that of premature separation of the normally implanted placenta, accounting for 58 cases, or 14.3 per cent of the series. As noted above, 20 of this group were associated with toxemia. One resulted from rupture of a cesarean scar, and another followed a fall. This is the only known case of maternal trauma associated with death of a fetus weighing more than 500 grams, among 34,368 such fetuses. The interval between fetal death and delivery was greater than one day in 22 instances and less than one day in 36 instances.

**4. Congenital anomalies and/or polyhydramnios.** Congenital anomalies were pri-

Table I. Cases of fetal death

Category	Cause	No. of cases	Per cent	No. of patients	No. of babies	No. of nulliparas	No. of this cause in other groups
1	Unknown	113	27.8	113	114	49	—
2	Toxemia	106	26.0	106	108	54	27
3	Abruptio placentae	58	14.3	58	59	25	1
4	Anomalies and/or polyhydramnios	45	11.1	44	45	18	7
5	Erythroblastosis	36	8.8	30	36	2	5
6	Cord accidents	27	6.6	27	27	16	9
7	Diabetes and sickle cell anemia	14	3.4	14	14	7	0
8	Amnionitis	4	1.0	4	4	0	0
9	External version	1	0.2	1	1	1	0
10	"Postmaturity"	3	0.7	3	3	1	13
	Total	407	99.9	400	411	173	62



Table II. Types of congenital anomalies

Type of anomaly	No.	No. with hydramnios
Anencephaly	15	7
Hydrocephalus	6	1
Congenital heart disease	5	1
Meningomyelocele	3	1
Multiple anomalies	3	1
Omphalocele	2	0
Chondrodystrophy	1	1
Diaphragmatic hernia	1	0
Encephalocele	1	0
Renal agenesis	1	0
Total	38	12

marily responsible for 38 or 9.3 per cent of these fetal deaths in utero; polyhydramnios was encountered in 12 of these cases. Polyhydramnios was also found in 7 other patients with apparently normal fetuses. Minor anomalies compatible with life were found in 7 other cases in this series, in which fetal death was attributed to other causes. The various types of anomalies are enumerated in Table II. The average gestational age at the time of fetal death was 35.7 weeks and the average interval between fetal death and delivery was 9.0 days.

**5. Erythroblastosis.** Erythroblastosis was encountered 36 times (8.8 per cent of the series) among 30 patients. Rh incompatibility was responsible for 34 cases, blood group incompatibility for two. Erythroblastosis caused fetal death in utero in one pregnancy out of 955 during the 10 years studied. Assuming an incidence of Rh incompatibility of 13 per cent among the Sloane Hospital patients, there was one intrauterine fetal death among approximately 130 pregnancies with an adverse Rh factor.

In one of these cases there had been no prior pregnancy; in another there had been only an early abortion. In 9 cases there had been one previous pregnancy, in 11 there had been two, in 8 there had been three, and in the remaining 6 there had been more than three. In 19 of the 34 parous cases there was a history of previous erythroblastotic stillbirth, and in at least 3 others there was a history of an erythro-

blastotic baby which survived. Six of the stillbirths in this group were hydropic.

The average time of fetal death was 33.8 weeks, the average number of days between death and delivery was 14.3.

**6. Cord accidents.** Cord accidents were thought to be the most probable explanation of intrauterine fetal death in 27 cases. Evidence of this was fairly conclusive in 19 and suggestive in the other 8. The nature of the cord accidents encountered in this series is depicted in Table III. Cord accidents were recorded in 9 other cases but were thought to have been of secondary or no importance. Cord accidents tended to occur quite close to term; in only 4 of these cases did the fetal death take place before the thirty-sixth week. Delivery took place within an average of 4.6 days.

**7. Concurrent medical diseases of the mother.** Fetal death was attributed to overt maternal diabetes in 9 cases, latent diabetes in 3, and sickle cell anemia in 2. Five of the 7 parous diabetic patients had had previous stillbirths. The average time of fetal death was 35.2 weeks, and the average interval between fetal death and delivery was 6.0 days.

**8. Amnionitis and congenital pneumonia.** Amnionitis, associated with premature rupture of the membranes, was thought to be responsible for 4 deaths. The membranes in these cases ruptured 3, 7, 9, and 11 days before delivery; 2 patients had received prophylactic antibiotics.

**9. External version.** External version at term in one case was followed by immediate

Table III. Types of cord accidents

Cord tightly around neck once	10
Cord tightly around neck twice	4
Prolapsed cord	3
Cord around neck 4 times	2
Two true knots in cord	2
One true knot in cord	2
Cord around neck 3 times	1
Cord around shoulder	1
Cord around neck twice and one true knot	1
Cord around neck once and one true knot	1
Total	27

Table IV. Cases of fetal death after the forty-first week

No.	Gestational age at time of fetal death (weeks)	Birth weight (grams)	Cause of fetal death
1	42	3,870	Probably pre-eclampsia
2	43	3,115	Probably pre-eclampsia (and omphalocele)
3	44	2,730	Probably multiple congenital anomalies
4	42	4,590	Probably congenital heart disease
5	42	3,300	Probably multiple congenital anomalies
6	42	1,650	Probably abruptio placentae
7	44	4,430	Probably cord around neck two times
8	45	3,000	Probably cord around neck four times
9	42	3,790	Possibly hypertensive cardiovascular disease
10	42	?	Possibly Rh incompatibility (in a para ii without antibody titer)
11	42	4,900	Possibly latent diabetes
12	44	4,400	Possibly latent diabetes
13	42	2,440	Possibly cord around neck once
14	45	4,050	Unknown
15	43	3,100	Unknown
16	43	3,140	Unknown

loss of the fetal heart tones and delivery of a macerated fetus 7 days later. No cord or placental accident was discovered at the time of delivery.

**10. Postmaturity.** Among the 407 cases in this series, fetal death occurred after the end of the forty-first week in 16 (Table IV). An analysis of the significance of postmaturity in these cases follows:

In 8 there was strong evidence that the fetal death could be attributed to one of the 9 other categories listed above; hence, these were omitted from this group. These 8 included one with abruptio placentae, 3 with fatal congenital anomalies, 2 with tight nuchal cords (one wrapped 4 times and the other wrapped 2 times around the baby's neck), and 2 with severe pre-eclampsia.

In 5 cases there was suggestive evidence that the fetal death could be attributed to another cause, so these were arbitrarily placed in the appropriate categories above. These 5 patients included one with moderately severe hypertensive cardiovascular disease, one with Rh incompatibility but no demonstrable antibody titer, 2 with latent diabetes, and one with the cord wrapped tightly around the baby's neck one time.

This leaves only 3 cases in which postmaturity was the only factor found which might have contributed to the fetal death.

**Relationship between time of fetal death and time of delivery**

When intrauterine fetal death is discovered during a given pregnancy it is impossible to predict when the conceptus will be expelled. This time interval is usually thought to be determined in part by the cause of fetal death and in part by the stage of pregnancy at which the fetus dies, but even these debatable generalities are of little significance in the individual case. The following data on this score were derived from this study.

Among the 58 cases of abruptio placentae, death of the fetus occurred at an average of 34.7 weeks and delivery took place within 48 hours in 47, within a week in 55. In 42 other cases, the duration of fetal death before delivery was unknown. With the exclusion of these 100 cases, the relationship between the time of fetal death and the interval until delivery is recorded in Table V.

In general, the earlier the fetal death the longer the interval until delivery. When fetal death occurred before the thirty-second week, delivery took place more than a week later in 36.9 per cent; between the thirty-third and thirty-seventh week, 23.3 per cent; between the thirty-eighth and forty-second week, 12.5 per cent. As can be readily seen from the table, however, this

Table V. Relationship between time of fetal death and time of delivery\*

No. of weeks gesta- tion at time of fetal death	No. of days between time of fetal death and delivery							Delivery delayed more than 1 week	
	1 or less	2-7	8-14	15-28	29-42	More than 42	Total	No.	%
Less than 32	20	33	10	5	9	7	84	31	36.9
33-37	24	65	14	10	2	1	116	27	23.3
38-42	40	41	12	3	3	0	99	18	18.2
More than 42	0	7	1	0	0	0	8	1	12.5
Total	84	146	37	18	14	8	307	77	25.1

\*Fifty-eight cases of abruptio placentae and 42 cases in which the duration of fetal death before delivery was unknown have been excluded from this table.

was no more than a faint trend, to which there were many exceptions.

As can be noted from Table VI, there is little correlation between the cause of fetal death and the interval until delivery. Fetal death due to toxemia, for example, is generally thought to be associated with imminent delivery. In this series 26.6 per cent of such patients were delivered more than a week later, which is not significantly different from the comparable figure of 25.0 per cent for the series as a whole. There seems to have been a slight tendency for deaths from erythroblastosis to occur earlier and for fetuses subjected to cord accidents to be delivered sooner.

It is sometimes said that regardless of when a fetus dies in utero, delivery will rarely be delayed beyond the estimated date of confinement. This was substantiated by

this study. Of the 200 fetal deaths which occurred prior to the thirty-eighth week, delivery was delayed beyond the fortieth week in only 2. One fetus died of erythroblastosis during the thirtieth week, and delivery was delayed for 13 weeks; another died of congenital anomalies at 33 weeks and was delivered 9 weeks later. Of the 107 fetuses in which death occurred after the thirty-seventh week, only 6 were delivered more than 2 weeks later.

The greatest interval between fetal death and delivery was 90 days (following death due to erythroblastosis at 30 weeks). There were 22 instances in which the interval exceeded 4 weeks, 8 in which it exceeded 6 weeks, and 4 in which it exceeded 8 weeks. The longer intervals were generally associated with fetuses weighing less than 1,000 grams.

Table VI. Time interval between fetal death and delivery

No.	Cause	Average duration of pregnancy at time of fetal death (weeks)	Average interval between fetal death and delivery (days)	No. of cases in which interval was unknown
1	Unknown (113)	34.5	7.9	24
2	Toxemia (106)	34.8	6.8	12
3	Abruptio placentae (58)	34.7	-	0
4	Anomalies and/or poly- hydramnios (45)	35.7	9.0	2
5	Erythroblastosis (36)	33.8	14.3	3
6	Cord accidents (27)	35.0	4.6	1
7	Diabetes and sickle cell anemia (14)	36.6	6.0	0
8	Amnionitis (4)	33.3	2.6	0
9	External version (1)	40.0	7.0	0
10	"Postmaturity" (3)	43.6	2.6	0
Total		35.1	7.9	42

### **Incidence of multiple pregnancies**

The ratio of multiple to single pregnancies in this series was 1:18.5. There were 18 instances in which one twin was lost (Twin A, 11 times; Twin B, 7 times), 3 in which both twins were lost, and one in which the first 2 of triplets were lost. An increased incidence of intrauterine fetal death in multiple pregnancies has been noted previously.<sup>8</sup>

The cause of fetal death was unknown in 12 cases, pre-eclampsia in 3, congenital anomalies in 2, abruptio placentae in 2, and hypertension, prolapsed cord, and amnionitis in one each. Nineteen fetuses were macerated, 3 were not macerated, and in 4 maceration was not mentioned.

### **Observations during labor and puerperium**

With regard to the management of intrauterine fetal deaths, there are a number of rather generally accepted obstetrical tenets; some are based on experience and others border on superstition. Among these are the impression that prolonged labor, postpartum hemorrhage, and puerperal sepsis are more commonly encountered; that the use of Pitocin holds great danger; that one should rarely do a cesarean section for a dead baby; and, more recently, that hypofibrinogenemia is more apt to occur. The following has been the Sloane Hospital experience in these matters.

Three hundred and eighty patients were delivered vaginally and 29 (7 per cent) abdominally. The indication for cesarean section was abruptio placentae in 16 and a uterine scar in 5. The remaining primary cesarean sections were done for placenta previa (3), cephalopelvic disproportion (1), transverse lie (1), eclampsia (1), abruptio placentae associated with erythroblastosis (1), and fetal distress in a viable twin (1). The uterus was removed at the time of cesarean section on 5 occasions.

Pitocin was used for induction of labor in 29 cases (7 per cent) and for stimulation of inert labor in 11 (2 per cent). No complications attributable to its use were noted.

Amniotomy was used to induce labor in 6 cases. Willett forceps were applied only once, and craniotomy was performed 5 times.

The duration of labor was recorded in 360 cases. Among 157 nulliparous patients, the length of labor exceeded 24 hours in only 8; among the 203 parous patients, labor exceeded 18 hours in only 8. No evidence of an unusual labor pattern was found.

The duration of ruptured membranes was recorded in 287 cases. In 251, the time interval was less than 2 hours; in 26 (9 per cent), it exceeded 30 hours. The incidence of ruptured membranes in excess of 30 hours for the service as a whole is 3.3 per cent. In 4 cases of amnionitis and 3 of prolapsed cord, premature rupture of the membranes was thought to have been indirectly responsible for the fetal death.

Postpartum hemorrhage was reported 25 times (6 per cent). In contrast, the incidence on the entire service is 3 per cent. Transfusion was not given to 5 of these patients; 500 c.c. of blood was given to 18; 1,000 c.c. to one; and 3,000 c.c. to one. Transfusion in 9 of these cases was necessitated by hemorrhage from abruptio placentae or placenta previa (the latter was the indication for transfusion in the patient who received 3,000 c.c.). Two of the others were given transfusions at the time of cesarean section and one for hemorrhage from a sulcus tear. Uterine atony was held responsible in only 3 cases, and anemia was incriminated in 5.

The syndrome of obstetrical hypofibrinogenemia had not been popularized during most of the time covered by this study. Hence, only one case was discovered; it was noted in the intrapartum period and was readily corrected by the administration of 2 Gm. of fibrinogen. The duration of fetal death had been only one day.

The febrile index, as defined by D'Esopo,<sup>2</sup> was calculated for all of the cases. The febrile index exceeded 25 in 104 instances (25.6 per cent). In a control group of 2,147 cases, this figure was exceeded in 276, or 12.8 per cent.



There were 4 cases of retained secundines treated by curettage, and another treated by oxytocics. Nine postpartum tubal ligations were performed.

### Comment

It is remarkable that more than one fourth of these fetal deaths were completely unexplained. If the mystery of these losses and the problem of toxemia are someday solved, these two steps alone should reduce the antepartum fetal mortality by one half.

The controversial syndromes of postmaturity and hypofibrinogenemia might also bear further comment.

The decision in Category 10, above, to attribute the cause of fetal death to postmaturity in only 3 of the 16 cases in which the fetus died beyond the end of the forty-first week may seem a little arbitrary. Most readers will probably accept the other causes indicated in the first 8 cases, wherein such severe fetal hazards as abruptio placentae were encountered. One can conclude, therefore, that postmaturity was the only factor implicated in the remaining 8 cases, or 1.9 per cent of this series. Since, however, this series also includes 113 cases of *unexplained* fetal death occurring *prior* to the forty-second week, it would seem even more arbitrary to place these 8 in a separate category, defined by gestational age alone. If we are to attribute these 8 cases to a syndrome which mysteriously appears after the forty-first week, then we should, with equal logic, assign these remaining 113 deaths to some unnamed syndrome which occurs before the forty-second week (Table VII).

With regard to the syndrome of hypofibrinogenemia in association with fetal death in utero, it is perhaps pertinent to

point out that, in this series of 407 cases (despite the fact that this syndrome was not well known during the period reviewed), there was no maternal death, and only one patient received more than 1,000 c.c. of blood. These data would suggest that this syndrome may be, if not rarer than, at least far less dangerous than some of the recent literature on this subject has indicated.<sup>5</sup>

### Summary

1. Four hundred and seven cases of antepartum fetal deaths are reviewed.
2. Fetal deaths attributable to (a) unknown cause, (b) toxemia, and (c) abruptio placentae were found to account for two thirds of the series.
3. The interval between fetal death and the onset of labor was found, in a definite but inconstant trend, to be inversely related to the gestational age of the fetus at the time of its death.
4. The incidence of puerperal morbidity was increased.
5. The incidence of postpartum hemorrhage was increased.
6. Management was essentially conservative.
7. Oxytocics, amniotomy, and cesarean section, when indicated, were employed.
8. The syndrome of postmaturity and hypofibrinogenemia are briefly discussed and their importance questioned.

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Table VII. Comparison of fetal deaths before and after forty-second week

	Explained	Unexplained
Before the 42nd week	277 (59%)	113 (41%)
After the 42nd week	13 (77%)	3 (23%)

# Stillbirth and ways to reduce it

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A. B. SIGALOV

THE aim of the present work is to study the causes of stillbirth and the possibility of eliminating them by means of improving the quality of the work of obstetrical-gynecological units.

We made a study of 810 pregnancies which terminated in stillbirths and which occurred over the course of a number of years in the obstetrical institutions of Stalinskaya Oblast. This was accomplished by means of an analysis of birth management through planned visits to various localities and by the study of annual reports and data obtained from a questionnaire which was worked out especially for this purpose.

All the pregnancies which terminated in stillbirth were discussed with the local physicians. As a result of these analyses we were able to note a subsequent improvement in all the figures for obstetrical work in the obstetrical-gynecological units. Thus, the stillbirth rate was reduced by 25 per cent among those born of full-term pregnancies and by almost twice as much among the prematurely born.

Of the 810 stillbirths, antenatal death of the fetus occurred in 30.6 per cent; intranatal, in 69.4 per cent. Antenatal death of the fetus attests the need for intensification of the work of obstetrical consultations for the detection of the toxemias of pregnancy as

well as extragenital and other diseases leading to the death of the fetus before the onset of labor. Measures for the elimination of intranatal death of the fetus represent one of the complex problems of obstetrics, the solution of which requires adequate training of obstetrician-gynecologists and midwives.

Among the stillborn infants, 68.7 per cent were full term and 31.3 per cent were premature. In the survey by Porembskiy,<sup>3</sup> these figures were 57 per cent and 43 per cent, respectively.

## Causes of stillbirth

According to the existing classification, we divided the causes of stillbirth into four groups: 31.5 per cent were due to maternal causes (Group I); 25.5 per cent to fetal causes (Group II); 17 per cent to placental causes (Group III); and 26 per cent to indeterminate causes (Group IV).

**1. Indeterminate causes.** The number of stillbirths from indeterminate causes (26 per cent) should be considered very high (14.1 per cent are indeterminate according to Keylin<sup>2</sup> and 4.39 per cent according to R. S. Kozina). Careful documentation of the management of labor (recording of labor activity and of changes in the fetal heart rate, notes of all examinations and operations made) and pathological examination of all stillborn babies should play an important part in the determination of the true cause of stillbirth; however, we had at our disposal the results of autopsies in only 61 per cent of cases. No autopsy was performed in the remainder.

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After analyzing the causes of stillbirth and taking into consideration the deficiencies in the work of the obstetrical institutions, we shall, in our further discussion, take the liberty of making a number of practical suggestions in the matter of the proper management of labor, which should, in our opinion, contribute somewhat to reducing the stillbirth rate.

**2. Maternal causes.** The maternal causes of stillbirth are presented in Table I.

From the point of view of the study of the causes of stillbirth and its reduction, prolonged dry labor, which occurred in 15.4 per cent of all the cases of stillbirth, is of great interest. Long duration of labor likewise exerts a significant effect in increasing the stillbirth rate, which coincides with data published by P. A. Beloshapko, M. M. Ginzburg, and S. L. Keylin.

Long, dry labors are often the result of poor work in the obstetrical institutions where physicians have not familiarized themselves sufficiently with modern methods of controlling labor. An individual approach to the management of labor should be incorporated into the practice of obstetrical institutions on a broad scale. This will include the application of anesthesia in some cases and the simultaneous acceleration or intensification of labor (methods of Khmelevskiy, Shub, and Kurdinovskiy-Shteyn) and, in other cases, giving the mother rest, building up her strength, and thus contribut-

ing to the restoration of normal labor. One of the measures used in protracted labor during the second stage, particularly in cases where there are defects in the abdominal wall, is the application of the Verbov binder which contributes to analgesia (Petchenko) and to shortening of this stage. Along with this, attention should also be directed to the problem of prophylaxis of intrauterine asphyxia of the fetus in cases of protracted labor, by means of the timely application of the A. P. Nikolayev method. This involves a systematic, frequent (every 10 to 15 minutes during the first stage and every 3 to 5 minutes during the second stage of labor) auscultation of the fetal heartbeat. Changes in the heartbeat urgently dictate the application of measures for combating asphyxia and, where necessary, for terminating labor.

A number of authors (S. L. Keylin, A. V. Lankovits, A. B. Sigalov) mention the high percentage of stillbirths in deliveries complicated by maternal disease and particularly by influenza and its complications. The instructions of the Ministry of Health, U.S.S.R., for combating influenza in the obstetrical institutions—timely and obligatory hospitalization of pregnant women who are ill and a high degree of aseptic precaution in the obstetrical institutions—should be carried out in these cases as measures directed at reducing the stillbirth rate. The use of antibiotics and sulfonamides should be considered obligatory in cases of infection in pregnant women.

As far as the toxemias of pregnancy are concerned (nephropathy of pregnancy, pre-eclampsia), the detection of the early forms of toxemias and the hospitalization of these patients contribute to reducing the number of stillbirths.

Stillbirth associated with a narrow pelvis can be prevented in many cases through the proper use of obstetrical consultations. The degree of constriction of the pelvis with consideration of the indications for operative delivery should be determined at the time of the obstetrical consultation, and pregnant women with this type of pathological condition should be sent to the hos-

Table I

<i>Causes of stillbirth</i>	<i>Per cent of the given group</i>	<i>Per cent of the number of stillbirths</i>
Protracted dry labor, primary and secondary uterine inertia	48.7	15.4
Toxemias of pregnancy	8.8	2.7
Acute, chronic, and febrile diseases	19.5	3.6
Cardiac disease	0.4	0.1
Cephalopelvic disproportion	18.0	5.6
Rupture of the uterus	3.1	1.0
Other trauma to the mother	1.5	0.5
Total	100.0	28.9

pital for delivery. With a detailed study of the pelvis and application of methods of functional diagnosis (measurement of the fetal head and study of the relations of the head to the pelvic diameters, Bastin's sign,\* the determination of progress of the head by external methods, x-ray examination, etc.), the proper management of labor in such an event should reduce the stillbirth rate.

**3. Fetal causes.** The fetal causes of stillbirths are presented in Table II. The data show that 7.5 per cent of all stillbirths are associated with breech presentations, 6 per cent with a transverse position of the fetus, and 4.5 per cent with multiple pregnancy. Adequate qualification of the obstetrical-gynecological personnel plays a particularly important part in reducing the incidence of stillbirths in this group.

Table II

<i>Causes of stillbirths</i>	<i>Per cent of the given group</i>	<i>Per cent of the number of all stillbirths</i>
Breech presentations	29.0	7.5
Transverse positions of the fetus	23.8	6.0
Multiple pregnancy	18.0	4.5
Monstrosities and developmental defects	16.2	4.2
Faulty engagements of the fetal head	10.0	2.5
Birth trauma	3.0	0.8
Total	100.0	25.5

Death of the fetus in breech presentations occurs for the most part at the time of extraction by the breech, very often inadvisedly, as well as through untimely or improper manipulation. The proper management of labor, with the application of the Tsov'yanov method in frank breech and footling presentations as well as the use of spasmolytic agents (1 c.c. of atropine solution 1:1,000 subcutaneously), should reduce the stillbirth rate.

Transverse presentations of the fetus re-

\*As given in the Russian: Vasten's.

quire a revision of the management of these cases. In the event of early loss of the amniotic fluid, one should refrain, if possible, from the Braxton Hicks version and, where the fetus is viable, resort to procedures which are less traumatic. Among these is the operation of metreurysis with subsequent version and extraction of the fetus under the appropriate conditions. Prolonged waiting during a dry period leads to a neglected transverse position and death of the fetus.

Stillbirth in cases of twins (usually, the death of the second fetus) is often caused by poor management of labor. Not all physicians have as yet familiarized themselves with the need for an active method of delivering the second fetus. Opening of the fetal sac with the administration of oxytocics or other procedures contributing to the rapid delivery of the second fetus (version and extraction of the fetus in the case of a transverse position, extraction of the fetus by the breech in pelvic presentations) is not always carried out in time after the delivery of the first fetus. With prolonged waiting for spontaneous delivery there is danger of death of the fetus from separation of the placenta as a result of a possible uterine contraction following the birth of the first fetus.

**4. Placental causes.** In Table III, causes of stillbirth resulting from changes in the placenta are presented.

Excessive conservatism is still encountered in the treatment of placenta previa. Pregnant women with symptoms of this condi-

Table III

<i>Causes of stillbirth</i>	<i>Per cent of the given group</i>	<i>Per cent of the number of all stillbirths</i>
Placenta previa	21.0	3.6
Premature separation of the placenta	13.0	3.2
Coiling of the umbilical cord	29.0	5.0
Prolapse of the umbilical cord	21.7	3.7
Hydramnios	10.9	1.9
True knot in umbilical cord, short cord	4.4	0.6
Total	100.0	18.0



tion are sometimes hospitalized late, and therefore some of them are admitted with considerable anemia from hemorrhage and frequently with a dead fetus. The operation of version with the cervix incompletely dilated, which for a number of reasons is still being used in certain obstetrical institutions for placenta previa, leads inevitably to the death of the fetus. In patients with marginal placenta previa Ivanov's method (scalp forceps) considerably reduces the stillbirth rate and is often effective as a means of stopping hemorrhage. In a whole series of patients with central placenta previa or with premature separation of a normally situated placenta, cesarean section performed in time saves both the mother and the fetus.

Coiling of the umbilical cord leads to stillbirth in a considerable number of cases. The difficulty of diagnosis does not permit the rendering of timely aid when needed. Careful and frequent auscultation of the fetal heartbeat aids in the detection of incipient asphyxia, and the administration of agents counteracting asphyxia (Nikolayev's triad) and the use of suitable operative procedures should reduce the incidence of stillbirth.

Vaginal examination, which contributes so much to the early diagnosis of complications of labor, including umbilical cord presentation and prolapse, is still not being used extensively in all the obstetrical institutions. This may explain the high percentage of stillbirths in the presence of complications. Where prolapse of the umbilical cord is diagnosed, operative delivery (version with extraction of the fetus, forceps, episiotomy) should be performed in time.

Incorrect management of labor in the case of hydramnios also contributes to stillbirth. Instead of watchful waiting in the first stage with cautious release of excessive quantities of amniotic fluid by puncture of the fetal sac after 3 to 3½ fingerbreadths' dilatation of the cervix, with the fingers introduced into the cervical canal, certain physicians use primarily oxytocics, which are not indicated in the given case. These incorrect tactics frequently lead to a precipitate discharge of amniotic fluid with pro-

lapse of the umbilical cord or of small parts of the fetus, which can result in stillbirth.

### Comment

In analyzing the procedures undertaken in complicated and pathological labors, we noted that in a number of institutions low forceps, the Ivanov method, the Tsov'yanov method, and the Verbov binder are not being used sufficiently at definite stages of labor in the presence of appropriate indications. Timely and correct application of the procedures mentioned would contribute to reducing the stillbirth rate. In certain cases (transverse positions of the fetus with early escape of the amniotic fluid, marginal presentation of the placenta), the operation of metreuryesis is indicated.

Familiarization of physicians with the proper management of labor is of great significance in the fight against stillbirth. Correct obstetrical tactics, should, when indicated, be combined with timely, cautious methods of operative delivery. In individual cases (incorrect position of the fetus and early escape of amniotic fluid, abnormality of labor in "elderly" parturients, unfavorable obstetrical history) where there is an insistent request by the parturient for a live fetus and in the absence of contraindications, recourse may be had to cesarean section.

As a result of our investigation we observed that the proper management of delivery (stimulation of labor, combating intrauterine asphyxia, timely, cautious, and correctly performed operative intervention) can prevent intrauterine death of the fetus in a number of cases.

It should be noted that the number of stillbirths which are preventable decreases from year to year, which is evidence for the increase in qualified aid for delivery. Nevertheless, the work of improving the qualifications of obstetrician-gynecologists and midwives should be continued on an even greater scale.

### Conclusions

1. Reduction in the rate of stillbirth is a problem of great, state-wide significance.

2. Among the causes of stillbirth, protracted dry labor constitutes a high percentage (15.4 per cent).

3. Transverse and pelvic presentations of the fetus occupy a considerable place also (13.5 per cent).

4. Improving the quality of obstetrical consultations is important in reducing the stillbirth rate.

5. Delayed diagnosis of birth complications, improper management of delivery, and appropriate obstetrical intervention undertaken late or incorrectly performed increase the stillbirth rate. To cope with this situation, the qualifications of obstetrician-gynecologists should be raised, and they

should be sent periodically to study the causes of stillbirth in the lying-in hospitals. The raising of the qualifications of midwives is also obligatory.

6. The main difficulty in the study of the stillbirth rate is the high percentage of so-called indeterminate causes, for the elimination of which careful documentation of the management of labor and autopsy of all stillborn infants should be made routine. The public health organizations should organize the pathology services of all large rayon centers and impose on them as a duty the detailed gross and microscopic pathological examination of the placenta, umbilical cord, brain, liver, etc., of the stillborn.

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# Cardiac resuscitation of the newborn infant

## Report of a case

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SHOULDER dystocia is an obstetrical emergency. With the stasis of delivery, the severe compression of the fetal chest by uterine contractions often results in cardiac arrest and death of the infant.<sup>1</sup> If cardiac arrest occurs, successful resuscitation may still be achieved if the resuscitation team works swiftly and vigorously.

The mother was a 32-year-old gravida iii, para ii, who had had 2 previous normal vaginal deliveries. Present prenatal course and early labor were uneventful. When delivery was imminent, the patient was taken to the delivery room and nitrous oxide-ether-oxygen anesthesia was administered.

The fetal head rotated from the left occipito-posterior to the left occipitoanterior position after several uterine contractions, and the head was delivered without difficulty after a small episiotomy was made. Immediate difficulty was noted when an attempt was made to proceed with the delivery of the shoulders.

As vigorous efforts at extraction were made, the infant remained thus, with head delivered and anterior shoulder impinged against the symphysis pubis, for 2 to 3 minutes. The infant made several gasping efforts during this time.

With maneuvering, the posterior shoulder of the infant was rotated 180 degrees anteriorly, allowing the shoulder which had been anterior and impinged to enter the pelvis in the posterior segment. The delivery was then rapidly completed.

It was apparent that the condition of the infant was critical and the obstetrician immediately noted that no heartbeat could be felt. By

use of an intermittent positive pressure breathing type resuscitator, the lungs were rapidly expanded several times. There was no improvement in the condition of the infant.

An incision was then made over the left fifth intercostal space anteriorly and extended until the heart could be palpated. The heart was in arrest, and immediate rhythmic compression was begun. At the same time, the intermittent rhythmic expansion of the lungs with oxygen was continued.

As the oxygenated blood was circulated by the rhythmic massage of the heart, improvement in the color of the infant's skin, lips, and nail beds was noted.

This resuscitation was continued for 3 minutes with no spontaneous cardiac action. Therefore, 0.5 c.c. of 1:1,000 epinephrine was injected into the myocardium. This produced an improvement in the tone of the heart, which had been flaccid, but no return of spontaneous cardiac action.

After another 2 minutes of resuscitation, another 0.5 c.c. of 1:1,000 epinephrine was injected into the myocardium. The heart began to beat spontaneously. As the beat became stronger, the assisting massage was discontinued. The chest was closed with underwater seal drainage. The stomach was emptied and secretions were removed from the tracheobronchial tree. At this time respiration was spontaneous and adequate.

The infant was transferred to an incubator in the nursery. He was crying and moving all extremities. His postoperative course was excellent and he was discharged 24 days after birth.

The baby is now 7 months old and appears to be a normal, healthy youngster.

## Summary and conclusions

A case of successful cardiac resuscitation of a newborn infant is reported. It appears

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that the principles of cardiac resuscitation which have been singularly successful in the treatment of cardiac arrest in the adult are equally applicable to the newborn infant. It is possible that some of the fetal deaths associated with shoulder dystocia may be

due to reflex cardiac arrest, and that more frequent cardiac resuscitation may save lives.

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# The incidence and prognostic implication of congenital absence of one umbilical artery

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ABSENCE of one of the 2 umbilical arteries from the entire length of the umbilical cord is a congenital anomaly that has been described only on rare occasions. Little attention has been paid to this malformation since the first comprehensive review of placental vasculature by Hyrtl<sup>1</sup> in 1870. Most observers have regarded this finding as an incidental curiosity of development which seemed to occur most commonly in association with acardiac twins.

In 1953 Benirschke and Brown<sup>2</sup> collected 55 cases from the files of the pathology departments of the Boston Lying-in Hospital and the Childrens Medical Center in Boston. They commented on the frequency with which fetal anomalies were associated with an absence of one umbilical artery. This series represented a retrospective analysis of highly selected pathologic material. From it the incidence of this anomaly could not be estimated and no appreciation could be gained regarding the distribution of normal versus abnormal fetuses. Therefore it appeared desirable to analyze a large series of consecutive placentas in a prospective manner. This study was undertaken with particular reference to the number of vessels in the umbilical cord and in an effort to detect malformation of the fetus at

the earliest moment. The early detection of certain congenital anomalies (e.g., esophageal fistula<sup>3</sup>) increases greatly the chance of survival of the affected newborn infant. Other aids, such as occurrence of hydramnios, have been used for the same purpose.<sup>4</sup> If the detection of congenital atresia of one umbilical artery could be shown to be of benefit to the treatment of newborn infants, close inspection of the cut end of the cord could be instituted easily as a routine procedure at delivery.

## Materials and methods

A series of consecutive placentas is being collected from the clinic patients of this hospital as part of the requirements for the collaborative study of factors responsible for cerebral palsy. This study was begun in August, 1957, and to date over 2,500 nearly consecutive placentas have come to examination. For the purpose of a minimum follow-up of 6 months, only 1,500 placentas have been included in this report. In addition, there is available material from 100 twin placentas which come from the ward and private services of this hospital. The examination consists of a gross evaluation of the placenta and a microscopic study of at least 3 blocks of tissue. These include sections of the middle portion of the umbilical cord, a segment of rolled membranes, and a section of full-thickness placental tissue. In the case of absence of one umbilical artery from the histologic section, the stored placenta is re-examined to verify absence of

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this artery from the entire length of the cord. In all instances of fetal death, autopsy confirmed absence of the intra-abdominal vessel as well. The pediatrician was informed in each instance of our finding and a "second look" was taken to detect possible congenital abnormalities of the infant which may have been overlooked on previous examination.

In addition to this group of consecutive and twin placentas, a large number of placentas from private deliveries is studied. This is done primarily in cases of fetal death, neonatal illness, or when maternal or obvious placental abnormalities prompt an examination. While this group is not the nucleus of the present report, reference will be made to the total number of umbilical arterial agenesis found in this laboratory.

Results

Fifteen placentas were found to lack one umbilical artery from the entire length of the umbilical cord. The number of the last case found was 1394, the next occurring is number 1590. The incidence of this anomaly therefore is approximately 1 in 100 preg-

nancies delivered past 20 weeks' gestation. The 15 cases are summarized briefly in Table I.

As in our previous report,<sup>2</sup> the male preponderance of Hyrtl's cases<sup>1</sup> is not borne out in this series. Only 5 of these infants were males. There was a nearly equal number of males and females in our previous series.

Three of the 15 cases were associated with severe malformations of the infant while minor abnormalities were noted in 4 of the other infants. One infant was stillborn and macerated but no congenital abnormalities were found in the infant at autopsy. Intrauterine asphyxia occurred as the result of massive infarction of the maternal surface of the placenta. This condition has been observed on several occasions in this laboratory and in 3 such instances has the cord lacked one umbilical artery. The cause of this infarction is not apparent. It has rarely been associated with toxemia and in several patients the same event took place in successive pregnancies. One wonders if some of the 13 cases of absent umbilical artery observed in abortuses by Javert<sup>5</sup> were

Table I

Case No.	Pathology No.	Sex	Twins	Gestational age (weeks)	Complications of pregnancy	Fetal anomalies	Follow-up
1	S57-1700	M		35	Chorioamnionitis	None found	Left town
2	S57-1760	F		39	Placental infarct	None found	Normal
3	S57-2168	F	Identical	38	None	Forked xyphoid	Normal
4	S57-2482	M		42	Irregular fetal heart, meconium discharge	None found	Normal
5	S57-2545	M	Identical	38	650 grams lighter than other twin	Hydrocele, abnormal rhythm	Normal
6	S57-3125	M		38	None	Club foot	Normal
7	S57-3221	F		40	None	None found	Normal
8	S58-644	F	Fraternal	38	None	Hyperetelorism, short fingers	No problem
9	S58-840	F		37	Hydramnios	Esophageal atresia and fistula, sacral anomaly	Operated, survived
10	S58-892	F		37	Hydramnios	Anencephaly	Stillborn
11	S58-1011	F		40	None	None found	Normal
12	S58-1162	F		40	None	None found	Normal
13	A58-62	M		37	None	Renal agenesis, atresia ani	Died
14	S58-1562	F		37	Maternal floor infarction, long cord	None found	Stillborn
15	S58-1912	F		40	Long cord	None found	Left town

not also associated with this type of placental infarction.

It is of interest that 3 of the infants in whom one umbilical artery was absent were one member of twins. Two of these were members of "identical twins" because of their monochorial placentation, and one was a dizygous twin. In a series of 100 unselected twin pregnancies from all patients of the Boston Lying-in Hospital which was collected over approximately the same period, one artery was missing in one member in 7 instances. This frequency would appear to represent a significant increase over the expected 1 per cent in random placentas even if one considered all twin pregnancies as "double pregnancies" and therefore doubled the number. A similarly unexplained observation from this institution<sup>6</sup> is the finding of a doubled incidence of fetal malformations in twin pregnancies. Four of the 7 twins were certainly monozygous because of monochorial placentation while 2 were dizygous because of difference in sex. One set of twins is isosexual but dichorionic and the zygoty cannot be determined in retrospect. Considering the fact that nearly 30 per cent of twins are monozygous but 4 of 7 twins lacking one artery were definitely "identical" one must come to the conclusion that the increased incidence of this vascular anomaly in twins is primarily due to its occurrence in "identical twins." This is not too surprising if one considers identical twinning as a malformation per se.

It should be emphasized again that these observations were made on routine sections through the midportions of the umbilical cords and that the cords were re-examined after the anomaly was found. On rare occasions the 2 umbilical arteries allegedly fuse somewhere in the umbilical cord but are present as 2 in the infant. None of the cases here reported showed this relationship. On the other hand, as has been pointed out by Hyrtl<sup>1</sup> and others, it is the rule that the 2 umbilical arteries fuse close to the surface of the placenta and then divide into the many chorionic branches.

In addition to the 55 cases reported previously<sup>2</sup> and the 15 cases from a consecutive series of placentas described in this study, we have found 43 other placentas lacking one umbilical artery. These were found in placentas submitted for consultation or associated with fetal disease, death, or placental and maternal abnormalities of the private service of this hospital. The total series of 113 placentas will be the subject of a more detailed study concerned with such data as maternal age, parity, placental abnormalities, and outcome of pregnancy.<sup>7</sup> At this time it is worth mentioning that among these 113 cases there were 58 offspring with major or minor congenital abnormalities. It thus appears that the finding of this cord abnormality signifies some discernible malformation in approximately half of the cases. The importance of its recognition is well illustrated by the following case report (Case 9 of Table I).

#### Case report

This baby girl was delivered in the thirty-seventh week of gestation of a healthy 26-year-old white gravida iii. The mother had 2 normal boys. Pregnancy was complicated by hydramnios during the last 2 months and by vaginal moniliasis. Because of the hydramnios, a flat plate of the abdomen was taken during the seventh month of gestation; this ruled out twin pregnancy and cranial malformation. No fetal movements were felt subjectively during the last 24 days of pregnancy. Labor began spontaneously and delivery was spontaneous. The baby cried within one minute. By bulb suction 2 to 3 c.c. of fluid was removed from the mouth, and "gastric" suction after delivery yielded 4 c.c. of fluid. The placenta did not appear abnormal. The baby remained flaccid, and 6 hours after delivery the baby was dusky and no meconium had been passed. Because of the apparent illness of the infant, a frozen section of the umbilical cord was requested by the pediatrician. This practice had been established in this laboratory to ascertain inflammation of the umbilical vessels as an index of intrauterine infection.<sup>8</sup> At this time it was also noted that the baby had excessive salivary secretion. The frozen section of the umbilical cord did not show evidence of inflammation, but only one umbilical

artery was found. Another attempt to pass a gastric catheter failed and on radiographic examination no air was found in the stomach. Also, an anomaly of the sacral bones was detected (absence of 2 left sacral rami and deformity of the corresponding vertebral bodies). Subsequently the infant was operated upon. A complete atresia of the distal esophagus with tracheo-esophageal fistula was found. Eight months after the procedure, the infant is continuing to progress satisfactorily.

### Summary

A consecutive series of 1,500 placentas has been examined with particular reference to the number of blood vessels in the umbilical cord. Complete absence of one umbilical artery occurred in 15 instances.

In 7 infants there were some congenital abnormalities noted on examination; 3 were of major character. One infant was stillborn. The anomaly occurred 3 times in one of twins. In a series of 100 twin placentas, one umbilical cord lacked one artery in 7 cases. The majority of these twins were monozygous.

It is concluded that the observation of congenital lack of one umbilical artery at the time of delivery may be of significant benefit to some affected infants by drawing attention to the possible presence of correctible congenital anomalies in the baby.

**Addendum.** Since the submission of this paper for publication, we have learned of a similar study of 1,200 placentas by Little.<sup>9</sup>

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# Primary ovarian pregnancy

## Report of two cases

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OVARIAN pregnancy, described by Tate (quoted by Guilford<sup>1</sup>) as "... rare as a blue lion or swan with two necks," probably occurs more frequently than previously realized. Even its presently estimated incidence of one in 25,000 pregnancies<sup>5</sup> might be increased by many authors<sup>2</sup> who take exception to the rigid pathologic criteria established by Spiegelberg<sup>3</sup> as necessary for diagnosis. These widely accepted criteria demand that the tube, including the fimbria ovarii, be intact and separate from the ovary; the gestation sac be in the normal ovarian position; the sac be connected to the uterus by the ovarian ligament; and unquestionable ovarian tissue be found in the walls of the sac. One of the cases reported below presents the "classical" symptomatic ruptured ovarian pregnancy with a fortunately clear and instructive picture of the pathologic condition involved; the other, probably logical extension of this pathologic condition when the conceptus develops to term.

**Case 1.** (University Hospitals of Cleveland No. 554-666.) P. R., a 29-year-old white married woman, was admitted to the hospital on Jan. 10, 1958, complaining chiefly of right lower quadrant pain of 3 hours' duration.

**Past history.** She had an appendectomy in 1949 and a lysis of abdominal adhesions in 1950. The menarche was at age 13 years with subsequent menstruation at intervals of 4 weeks with a duration of flow of 5 days. There was an

associated moderate dysmenorrhea. She was para iii and had previously had 2 full-term deliveries and one miscarriage at about the sixth week.

**Present illness.** The last menstrual period was on Nov. 24, 1957, 6 days earlier than expected but otherwise normal. Vaginal spotting occurred on December 25 and 27. She had no symptoms usually associated with pregnancy but denied having these when previously pregnant. During the night preceding admission she passed urine 4 times. Three hours previous to admission she experienced the sudden onset of continuous sharp right-sided abdominal pain which became progressively worse and generalized through the lower abdomen. Pelvic examination 2 hours before admission revealed right adnexal fullness.

**Physical examination.** Besides a moderate tachycardia of 100, the vital signs were normal. The patient was pale and lay in bed complaining of lower abdominal pain exacerbated by motion and partly relieved by flexing the thighs. When she sat up for examination she experienced dizziness unaccompanied by tachycardia or sweating. The breasts were not engorged and no fluid could be expressed. Bowel sounds were normal. The scaphoid abdomen was soft but tender to palpation in the right lower quadrant. The rebound tenderness present was referred to this area. Muscle spasm, abdominal rigidity and costovertebral angle tenderness were absent and there was no shoulder pain.

Apart from leukocytosis of 15,000 and a moderate anemia of 9.7 Gm. hemoglobin there were no demonstrable abnormalities of blood or urine.

On examination under anesthesia 2 hours later no blood or discharge was found in the vagina nor was there vaginal or cervical cyanosis. The cervix was firm and multiparous. The fundus was anterior, of normal size and shape. A definite single right adnexal mass about 4 cm. in diameter was palpable and considered

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consistent with an enlarged ovary. The left ovary was not enlarged. Upon colpocentesis in the posterior midline free unclotted blood returned. Preoperative diagnosis was ruptured extrauterine pregnancy.

**Operation.** The abdomen contained 300 to 400 c.c. of fresh and clotted blood. The left tube and ovary appeared normal. The right tube was also free and intact, but the right ovary, which was in normal position, presented a 2 cm. ulcerated area which appeared to be a ruptured corpus luteum cyst with a small blood clot adherent at the site of interruption. The remainder of the ovary was grossly normal. The corpus luteum was excised and the edges brought together with plain catgut sutures. All blood clots were saved for pathologic study. The appendix was not present and the other organs appeared normal. The postoperative course was uneventful except for 4 days of vaginal blood loss. The patient was discharged 7 days later.

**Pathologic findings.** Fig. 1 shows a cross section of the resected portion of the right ovary, including the ruptured, hemorrhagic chorionic vesicle. The corpus luteum of pregnancy is conspicuously defined. The vesicle, almost completely surrounded by ovarian tissue, is shown in more detail in the low-power photomicrograph (Fig. 2). Here the rupture site is evident and the continuation of the ovarian germinal epithelium over the surface of the gestation is well defined. Fig. 3 shows clearly the placental villi in relation to the corpus luteum, the intervening zone being infiltrated with a moderate number of polymorphonuclear leukocytes.



Fig. 1. Gross specimen of corpus luteum and chorionic vesicle.

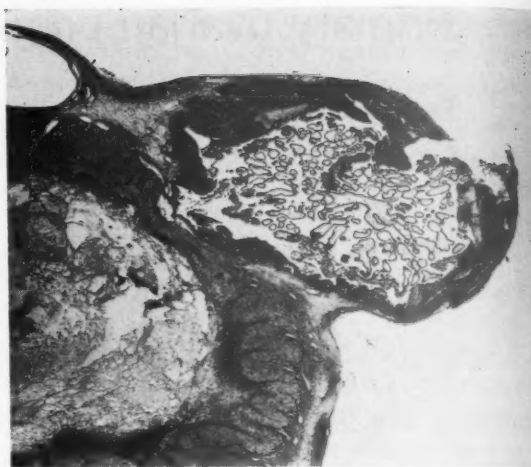


Fig. 2. Low-power photomicrograph of Fig. 1.

**Case 2.** (University Hospitals of Cleveland No. 685-820.) A 22-year-old married Negro woman was admitted to the hospital on Feb. 5, 1957, complaining chiefly of lower abdominal pain and a faint feeling for the previous 8 hours.

**Past history.** She had had pelvic inflammatory disease in 1956. She was a para ii and had previously had one premature and one full-term delivery.

**Present illness.** The last menstrual period was on Dec. 23, 1957, and was 2 days shorter than usual but otherwise normal. Vaginal spotting occurred twice in October and once in early November. On November 4 she was seen in the Emergency Ward complaining of lower abdominal pain and fever. A leukocytosis was noted but following treatment for pelvic inflammatory disease the symptoms subsided. At that time the uterine size was estimated to correspond with that observed at the twelfth week of pregnancy. She was admitted to the hospital on November 26 complaining of lower abdominal pain and vaginal spotting. Examination under anesthesia revealed a firm cystic mass thought to be the uterus enlarged to the size of a 20 weeks' gestation. Abdominal radiography revealed probable intrauterine gestation and the frog test for pregnancy was reported as being positive. Hemoglobin was 10 Gm. The patient was discharged when the pain subsided. Two months later, on Jan. 21, 1958, she was readmitted complaining once again of lower abdominal pain and vaginal spotting. Hemoglobin was now only 6.4 Gm., hematocrit 23.5 per cent. The anemia was slightly hypochromic, microcytic type and was accompanied by reticulocytosis.

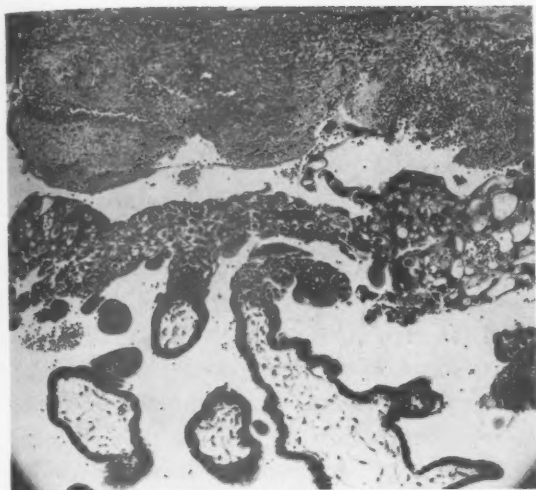


Fig. 3. High-power photomicrograph of Fig. 1.

toxicosis. Extensive hematologic investigation revealed no evidence of hemolysis; no site of extensive external blood loss could be demonstrated. During this time the hemoglobin fell to 4.9 Gm., then rose to 7.4 Gm. on ferrous sulfate therapy. No blood was obtained on needle colpocentesis. When the abdominal pain subsided and the hemoglobin stabilized, the patient was discharged. Three days later, however, the pain recurred; the patient felt faint and nauseated and was again admitted to the hospital.

**Physical examination.** The patient was afebrile and had a tachycardia of 100 with normal blood pressure and respiration. She was a pale Negro woman moderately distressed by lower abdominal pain. The skin was peripherally cold and clammy but centrally warm and there was no sweating. The breasts were engorged. The heart was not enlarged but a gradual harsh systolic murmur was heard at the apex. The bowel sounds were normal. The abdomen was distended by the uterus with what was thought to be fundus being palpated 28 cm. above the symphysis. Although no definite fetal parts were palpable, the fetal heart was heard in the right lower quadrant at a rate of 124 per minute. On sterile vaginal examination no blood was found, the cervix was 3 cm. effaced but tightly closed.

The hemoglobin, however, was now only 6.4 Gm., hematocrit only 25 per cent. Except for a moderate leukocytosis of 12,000, blood and urine examinations were normal.

**Operation.** The abdomen was found to contain numerous fresh and old blood clots. The pelvic organs presented a large, left-sided, white

cystic structure having a rupture at its superior pole, from which fluid and a viable fetus escaped upon manipulation. The cord was clamped and tied and the infant delivered. Further examination of the mass revealed it to embrace the left ovary and tube and round ligament and to be intimately associated with the entire left posterior and lateral aspect of the uterus. The mass was separated from the denuded uterine wall and, following resection and ligation of the left infundibulopelvic ligament, removed from the abdomen. The defect in the myometrium was closed and the patient had an uneventful recovery.

**Pathologic findings.** The tissue mass weighed 840 grams and measured 15 by 15 by 8 cm. A placenta and umbilical cord were identifiable within the specimen. There was a large (over 500 c.c.) retroplacental hematoma. No ovary or definite tube could be grossly identified; a cordlike structure, possibly round ligament, was present. Numerous sections, for example, Fig. 4, showed a fetal sac intimately related to and partly composed of ovarian tissue. The section demonstrates the definite invasion of ovarian stroma and the relation of the chorionic villi and trophoblastic tissue to the ovarian tissue. Other sections show an apparently normal Fallopian tube and a fibromuscular structure thought to be round ligament. At no point in any of these sections, however, did the fetal sac invade these tissues.



Fig. 4. Low-power photomicrograph of relationship of placenta to ovarian stroma Case 2.

**Comment**

Clinically, these cases illustrate the difficulty in distinguishing ovarian from other forms of ectopic pregnancy. The predominant features in Case 1 were lower abdominal pain and abnormal vaginal bleeding, symptoms present in 10 to 70 per cent, respectively, of the cases reported by Taber and Crossett.<sup>5</sup> These authors' statistics accent the unreliability of a missed menstrual period, as occurred in our patient, as a *sine qua non* to the diagnosis. In 44 per cent of their cases, symptoms occurred within 28 days of the previous normal period. The patient in Case 2 also presented the 2 cardinal symptoms of ectopic pregnancy, namely, abdominal pain and abdominal vaginal bleeding. Both, however, were clinically overshadowed by the more dramatic picture of blood loss. The diagnosis was clinically obscure and became evident only after investigation excluded other causes of the anemia such as external bleeding or hemolysis. Intra-abdominal hemorrhage, possibly from partial abruption of an abdominal implantation, was suggested by the correlation in time between the episodes of abdominal pain and the decrements in hemoglobin.

Pathologically, we believe Case 1 presents an exceptionally clear illustration of the "extrafollicular" type of ovarian pregnancy. From the operative findings—the tube intact and separate from the ovary, the gestation sac and ovary in the normal ovarian position, and the ovary connected to the uterus by the ovarian ligaments—and from the clear microscopic demonstration of ovarian tissue in the wall of the gestation sac, this case completely satisfies the rigid criteria established by Spiegelberg.

Case 2 is less definite. Several other reported cases of ovarian pregnancy<sup>4</sup> have developed to term. In the present case, although the criteria would be met, the tube could not be plainly identified and grossly separated from the ovary. Therefore, tubo-ovarian gestation cannot be ruled out. But this is only negative evidence. The fact that this gestation progressed to viability and the fetal sac structures to a 28 weeks' size, plus the microscopic presence of the Fallopian tube and the failure to demonstrate evidence of microscopic invasion of the tube or other structures by embryonic tissues, provides strong evidence that the pregnancy was ovarian in site and represents but a progression of the clear pathologic findings in Case 1.

**Summary and conclusion**

Two cases of primary ovarian gestation are reported. Early rupture makes this condition difficult to distinguish clinically from other forms of ectopic pregnancy. Pain and abnormal bleeding are the most common clinical manifestations; a missed menstrual period occurs in only about half of the reported cases. Progress of the gestation to viability and partial placental separation result in a clinical picture indistinguishable from other types of intra-abdominal bleeding. The pathology following the early rupture could clearly be demonstrated in one case; that of more sustained gestation less clearly in the other. The difficulties in applying rigid criteria for ovarian implantation in cases proceeding to viability are discussed.

I wish to thank Dr. William C. Weir for permission to use his private case (Case 1) in this presentation and Dr. Leslie Duncan for helpful editorial criticism.

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# Cervical pregnancy

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CERVICAL pregnancy has been reported increasingly often since the turn of the century—though not so often that it does not remain a surprise to each physician who encounters it.

Rubin,<sup>1</sup> in 1911, defined the pathology in the U. S. literature, writing on a case of cervical pregnancy that had been separately reported by Goodman.<sup>2</sup> Studdiford,<sup>3</sup> in 1945, was more strict in differentiating isthmico-cervical pregnancies and compiled 28 cases reported to his satisfaction. Of the 28, 14 were pathologically diagnosed and 14 clinically diagnosed. Schneider,<sup>4</sup> in 1946, insisted on a more rigid limitation of the diagnosis to cases in which nidation in the cervical canal could be assumed. Using his criteria he found the condition more rare than did Studdiford. The matter of strict definition aside, the consensus is that trophoblastic invasion of the cervix proper is a condition which in all likelihood will call for one or more units of blood before it is corrected.

Studdiford noted that at the time of his report the standard texts gave little or no space to the subject of cervical pregnancy—or indeed denied its existence. A recently published text<sup>5</sup> devotes a whole page to the now well-documented entity and endorses the treatment proposed by Morton<sup>6</sup> in 1949. Recognizing, as did Studdiford, that the cervical placenta has certain of the features of placenta accreta, Morton suggested, "separation of the placenta is to be avoided and the placenta might profitably be packed

against the cervical wall." This treatment could be used only if the diagnosis is made before removal is attempted. We are aware of no report of the use of this method to date.

The hemorrhage accompanying attempted removal of the cervical placenta is a vivid part of the reported cases, with the exception of those of Ellingson,<sup>7</sup> Duckman,<sup>8</sup> and Flanagan and Walsh.<sup>9</sup> It has usually been at the time of this hemorrhage that the correct diagnosis first struck the obstetrician. The following case report is no exception.

A 40-year-old married white woman, gravida v, para ii, who had had 2 abortions, was admitted to Nassau Hospital on Sept. 9, 1957, because of vaginal bleeding. Her last normal period had started on July 17, 1957. From August 16 until August 19 she had cramps and passed small clots along with a menstrual-like flow. Throughout the remainder of the month she experienced low backache, weakness, and a drawing sensation in the lower abdomen.

On the day of admission she began a bright red flow. She attempted to insert a tampon but was unable to do so because of a "mass" in the vagina. Bleeding became heavy and she called her doctor who advised admission to the hospital.

Her past history included an ovarian cystectomy 3 years previously and repeated bouts of cystitis in the past year.

When seen in the hospital the patient had moderately heavy bright vaginal bleeding but no pain. She appeared to be a well-developed, well-nourished white woman in no acute distress. Vital signs were: pulse 80, respirations 20, temperature 99, and blood pressure 130/80.

Physical examination revealed no abnormalities except for a large, soft, blue cervix. The cervix was closed and bleeding came from

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within the os. At this point it was felt that the patient was pregnant and that the bleeding was due to varicosities of the cervix. A vaginal pack controlled the bleeding. The pack was removed in 24 hours and, with no further staining, the patient was discharged on the third day.

On Oct. 4, 1957, the patient was readmitted having had 2 episodes of heavy bleeding that day. On admission she appeared pale and was weak but in no pain. Her vital signs were: pulse 65, respirations 20, blood pressure 70/40, and temperature 98.6° F. Urinalysis was normal except for a trace of albumin and 3 to 5 red blood cells per high-power field. The hemoglobin was 9.8 Gm. and hematocrit 28 per cent. White blood count and differential were normal.

In view of her condition and the continuing profuse bleeding, she was immediately prepared for curettage—the diagnosis being inevitable abortion of a 10 weeks' pregnancy.

Examination in the operating room revealed the vagina to be filled with clots and fresh blood. Bimanual examination revealed what was felt to be a soft, slightly enlarged uterus surmounted by a firm fibroid the size of a normal uterus. The cervix was thin and the external os was dilated to 3 cm. The products of conception protruded from the os. The cervix ballooned out, having a cavity 5 cm. in diameter. The posterior wall of the cervix was extremely thin and was the site of placental attachment. The internal os was closed. Stubbornly adherent placental tissue was removed with ovum forceps and a sharp curette, and bleeding became brisk. Sutures were placed in an attempt to ligate the cervical branches of the uterine arteries, and a tight pack was inserted in the cervix and vagina. The patient received 500 c.c. of Dextran, 1,000 c.c. of whole blood, 500 c.c. of dextrose and water, and 1,000 c.c. of dextrose and saline during the first 12 hours in the hospital. She bled through the packing, but drainage soon became scant and she maintained a blood pressure of 100/60 to 112/70 with a pulse of 96. On Oct. 5, 1957, the day following curettage, the hemoglobin was 7.7 and the hematocrit 24 per cent. Despite Ergotrate and Koagamin she again developed bright red bleeding through the pack. She received another 1,000 c.c. of blood on October 6, but with continued bleeding a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on October 7. She received 1,500 c.c. of blood during the procedure.

The pathologist described the uterus as weighing 310 grams. The site of placental attachment was 5 to 6 cm. in diameter; it was high in the cervix and was covered with blood clot and necrotic tissue (Fig. 1). The wall of the cervix beneath the placental site was very thin. The pathological diagnosis was "tubes, ovaries, and uterus with cervical pregnancy."

The patient had a benign, afebrile postoperative course and was discharged on the eighth postoperative day. The hemoglobin level on discharge was 11.7 Gm. and the hematocrit was 41 per cent.

### Comment

In 1945 Studdiford compiled 14 pathologically diagnosed and 14 clinically diagnosed cases of cervical pregnancy. There were 6 deaths in this group.

In 1953 Baptisti reviewed the literature and compiled an additional 17 cases, 3 pathologically and 14 clinically diagnosed. In this group there was one death.

Seven additional cases have been reported since 1953, as noted in Table I. Four were pathologically and 3 clinically diagnosed. There were no deaths in this group. The improved mortality has been attributed to the use of blood transfusions when needed in the cases since 1945.



Fig. 1.

Table I. Cases of cervical pregnancy reported since 1953

<i>Date reported</i>	<i>Author and reference</i>	<i>Patient's age</i>	<i>Gravidity</i>	<i>Parity</i>	<i>Length of pregnancy (weeks)</i>	<i>Transfusion (c.c.)</i>
1954	Burstein <sup>12</sup>	21	i	0	16	1,500
1954	Cave <sup>14</sup>	45	iv	iii	10	1,500
1954	Flanagan and Walsh <sup>9</sup>	?	iii	i (1 abortion)	10	yes
1955	Bachman <sup>13</sup>	24	ii	i	16	4,500
1955	Cummin <sup>11</sup>	20	ii	i	12	500
1957	Schneider and Dreizin <sup>4</sup>	34	vii	i (5 abortions)	12	1,500
1959	Sherwin and Berg	40	v	ii (2 abortions)	10	3,500

The clinical picture of cervical pregnancy has included the following:

**Usually.**

1. Patient in older childbearing age group.
2. Early, painless bleeding (occasionally with no history of amenorrhea).
3. Termination in the first trimester because of hemorrhage.
4. An enlarged, ballooning cervix with the external os slightly dilated and membrane or tissue visible on speculum examination.
5. Placental tissue adherent to the cervix, producing heavy bleeding on attempted removal.
6. Shock and hemostasis present shortly as difficult problems.

**Often.**

1. Low backache and lower abdominal pain.
2. Undue delay in completion of what appears to be an inevitable abortion.
3. A palpable, fibroidlike, firm uterus atop a soft cervical mass.

**Rarely.**

1. Urinary retention and tenesmus.

Schneider adds to the above the likelihood of secondary hemorrhage up to 6 weeks after curettage.

Successful treatment following curettage has included packing, packing and suturing of the cervix, partial and total resection of the cervix, vaginal hysterectomy, supravag-

inal hysterectomy, and total hysterectomy. Trial of conservative treatment has been urged since many of the patients treated without hysterectomy have gone on to one or more uncomplicated pregnancies. No report of a case treated without attempted removal but rather packed to await resorption of the placenta accreta-like tissue has been found.

Cases progressing beyond 4 months, according to Studdiford, would be expected to yield only to hysterectomy.

It would appear that the present availability and use when needed of adequate blood transfusions has been responsible for the decreased mortality in the cases since 1945.

To the excellent bibliographies of Baptisti<sup>10</sup> and Schneider<sup>4</sup> we would add the references listed at the end of this paper.

**Summary and conclusion**

Cervical pregnancy continues to appear as a rare but troublesome booby trap, usually triggered by attempts to complete what appears to be the cervical stage of an abortion. An additional pathologically diagnosed case is presented in evidence of this conclusion.

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# Coexistent interstitial and intrauterine pregnancy following homolateral salpingo-oophorectomy

## Report of a case

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COMBINED intrauterine and extrauterine pregnancies have been frequently reported. Devoe and Pratt<sup>2</sup> reported 395 cases and Winer<sup>5</sup> added 71 cases from a review of the world literature and from their own experience. It has been estimated that combined pregnancy occurs once in every 30,000 gestations.<sup>5</sup>

Many theories have been advanced explaining the etiology of combined pregnancy. It is assumed that this occurs with fertilization of two ova. Any condition which impedes the progress of one of the fertilized ova through the tube predisposes to heterotopic pregnancies. Most frequently the second pregnancy is located in the tube.

Interstitial pregnancy following homolateral salpingectomy is rare. The incidence has been variously estimated as one in 10,000 to one in 45,000 pregnancies.<sup>1</sup> The pathogenesis seems to be either internal or transperitoneal migration of the fertilized ovum.

The following is a case report which we feel represents a case of internal migration. A pregnancy existed both in the uterus and in the interstitial portion of a previously excised tube. The literature shows no similar case.

### Case report

**Present illness.** N. L., a 26-year-old white woman, gravida v, para iv, entered the hospital

because of right lower quadrant abdominal pain of 4 days' duration.

The patient's last normal menstrual period occurred 4 months prior to admission. Twenty-six days later she had a 2 day episode of bloody vaginal spotting. She subsequently developed swelling and tenderness of her breasts and considered herself pregnant.

Two weeks prior to admission she noted an asymptomatic mass in the right lower quadrant of her abdomen. During the next 10 days it slowly increased in size. Four days before admission the patient noted a dull nonradiating pain in the area of the mass. The pain became progressively more severe until she was hospitalized.

**Past history.** Three years previously, the patient had had a right salpingo-oophorectomy because of a tuboovarian abscess. A cornual resection of the interstitial portion of the tube was performed (Fig. 1). No other pelvic abnormalities were noted. Past history was otherwise essentially negative. The patient had had 4 full-term pregnancies all of which had terminated in vaginal delivery.

**Physical examination.** The patient was a well-developed, well-nourished white woman in moderate distress due to abdominal discomfort. Findings were unremarkable except for the abdomen and pelvis. There was a right lower quadrant mass that was moderately tender. It was about 8.0 cm. in diameter and appeared to be a part of the uterus. This was confirmed on bimanual pelvic examination. The uterus was about the size of a 4 months' pregnancy and was soft. A mass projecting from the right side of the fundus was of the same consistency as the rest of the uterus. No other abnormalities were noted.

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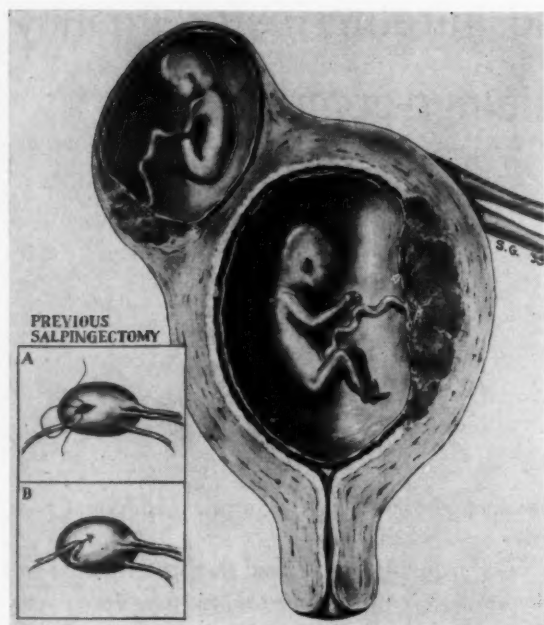


Fig. 1. Artist's conception of sagittal section of uterus. Inset shows utilization of the round ligament to reinforce defect in uterine cornu.

**Laboratory data.** Hemoglobin on admission was 11 Gm. per cent; hematocrit 36 vol. per cent; white blood count 10,850 with a normal

differential. The sedimentation rate was 28 mm. per hour. The serology was negative. Urinalysis and serum electrolytes were within normal limits.

**Hospital course.** On the first and second hospital days the patient had a small amount of bloody vaginal spotting. The right lower quadrant pain became more severe. On the third hospital day she was taken to the operating room with the preoperative diagnosis of intrauterine pregnancy with impending rupture through the site of the previous salpingectomy. Upon laparotomy the patient was found to have an interstitial pregnancy at that site. She also had an intrauterine pregnancy (Fig. 1). The interstitial pregnancy was excised without entering the uterine cavity. The intrauterine pregnancy was left intact.

Postoperatively the patient's vaginal bleeding at first became more profuse and then subsided. On the fifth postoperative day she again began to bleed. Soon after, she passed a fetus vaginally. She was taken to the operating room for dilatation and curettage of the uterus. She was discharged from the hospital 3 days later, 8 days after the laparotomy.

**Pathologic report.** The fetus of the interstitial pregnancy measured 8.0 cm. crown to rump. The other fetus measured 10.0 cm. Both were male.

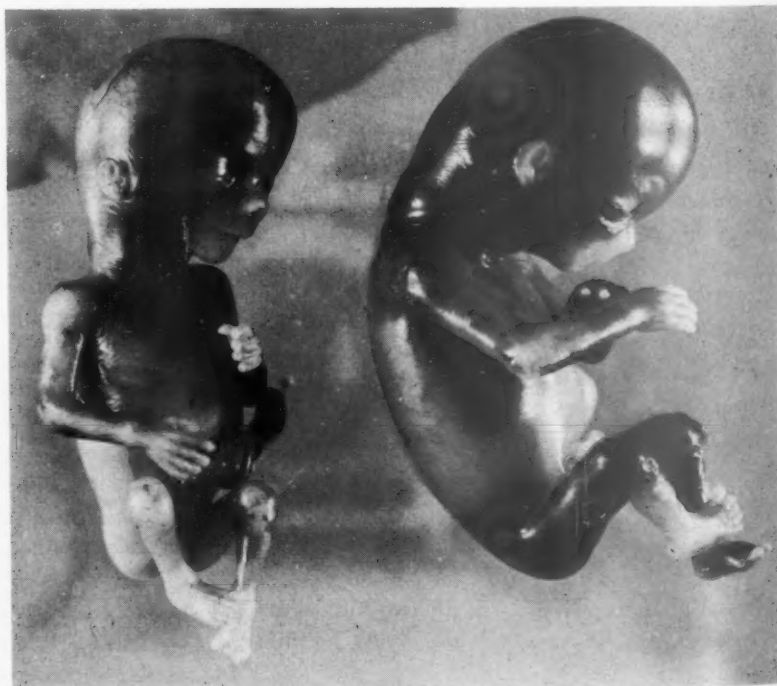


Fig. 2. Comparative sizes of fetuses. Left, interstitial, 8 cm. long; right, intrauterine, 10 cm. long.

### Comment

Fig. 2 shows a definite difference in the size of the two fetuses. We offer two possible explanations for this. If both ova were fertilized at the same time, gestation for both pregnancies would be the same.

It could then be postulated that the difference in growth in the ectopic location was due to a less efficient placental circulation, since the uterine wall in this area was thinner.

If, however, the ectopic gestation resulted from a later fertilization then the difference in size would be due to the shorter duration of that pregnancy and the phenomenon of superfetation would exist. The mechanism for this would be either transperitoneal or intrauterine migration of the fertilized ovum with implantation in a uterus containing a pregnancy of at least one month's duration. Intrauterine migration is possible even in the presence of an intrauterine pregnancy.<sup>3</sup>

There are no recorded proved cases of superfetation in the literature. Although superfetation is theoretically possible up to the third month of gestation since fusion of the decidua vera and reflexa occur at that

time, the marked inhibition of ovulation which exists during pregnancy makes this unlikely. Studdiford<sup>4</sup> suggests that the reported cases of superfetation represent abnormal development of one fetus of a twin pregnancy. The majority of cases described resulted in abortions in which one fetus was considerably smaller. In order for superfetation to be proved conclusively, the pregnant woman must deliver two fetuses of widely differing size, appearance, and development. The placenta of both fetuses must be healthy and normal.

There is no wide divergence of fetal size and development in the case herein presented, and in our opinion it does not represent a case of superfetation. It is presented merely as an unusual example of a twin pregnancy.

### Summary

A case of coexistent intrauterine and interstitial pregnancy following homolateral salpingectomy is presented.

The possible mechanism for this occurrence is discussed.

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# Eclampsia without convulsions

Eclamptic lesions in fatal maternal cases  
with and without clinical pre-eclampsia

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THE traditional concept of eclampsia as defined by Eastman<sup>1</sup> is: "An acute disease peculiar to gravid and puerperal women which is characterized by clonic and tonic convulsions during which there is loss of consciousness followed by more or less prolonged coma." Whether or not convulsions are a part of the clinical picture of severe toxemia is of very little real importance, but their presence has served to demarcate those cases which are more severe or fatal from those that are less severe and nonfatal. In this country the nomenclature has been governed by the symptom of convulsions. Indeed, the presence of convulsions is generally taken to mean "eclampsia" and possible death whereas its absence connotes "pre-eclampsia" and a lesser likelihood of death. How, then, does one classify the patient who dies with autopsy evidences of eclampsia, even though convulsions have not occurred?

This confusion in nomenclature has been responsible for the adoption of the term "eclampsia without convulsions." It has heretofore invariably been a necropsy diagnosis. The criteria necessary to establish the diagnosis have been laid down by such

writers on the subject as Schmorl<sup>2,3</sup> and more recently by Sheehan.<sup>4</sup> Fifty years ago Schmorl stated, "The morphologic changes in the liver are so characteristic for eclampsia that even in cases of eclampsia without convulsions the diagnosis of eclampsia can be made on the basis of these changes alone." The pathologic changes characteristically occur in the liver, as periportal necrosis and hemorrhage and, usually, hemorrhage or fibrin thrombi in the sinusoids in these areas, in the kidney, as enlarged ischemic glomeruli with fine fibrils formed under the thickened basement membrane of its loops, and in the brain as macroscopic cerebral hemorrhages, softenings, or meningeal hemorrhages.

In 1944, Reis and Bernick<sup>5</sup> reported one case, bringing the total to 45 reported cases of eclampsia without convulsions and to 9 cases of eclampsia without either convulsions or coma. Their patient, however, had no hypertension and no convulsions or coma. Previously, Coffiere<sup>6</sup> and King<sup>7</sup> had each reported a case and reviewed the literature. In 1952, Dieckmann,<sup>8</sup> in attempting to correlate the findings of various authors, came to the conclusion that many of the pathologic changes described are attributable to causes other than eclampsia. In this group of patients are several who died without convulsions and others whose unexplained deaths occurred in labor or shortly after delivery. A few of these may have been due to pul-

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monary emboli of amniotic fluid and its contents. Contrary to others, Dieckmann stated that he did not believe that there was any pathologic lesion that is characteristic of this disease. Together with Wegner<sup>9</sup> he reported the eighth case of eclampsia without convulsions or coma in the literature. In the past few years a few scattered reports of eclampsia without convulsions have appeared, the evidence being based upon pathologic findings.

At the Cook County Hospital the autopsy material of a 9 year period from 1946 to 1955 was carefully reviewed and the findings cross-indexed. This has helped to focus our attention upon 7 fatal cases in which the pathologic conditions described resembled those in the cases which Sheehan<sup>4</sup> labeled "eclampsia" because of the findings that he considered as pathognomonic of this disease. All of the cases selected were without convulsions, and two showed no evidence of pre-eclampsia clinically. During this period of time there were 88,690 deliveries at the Cook County Hospital and 196 cases in which eclampsia without convulsions occurred. Thus, the ratio of convulsive to non-convulsive eclampsia was 196:7, or an incidence of 3.57 per cent. Similarly, the incidence of eclampsia to the total number of deliveries was 0.2 per cent and the incidence of eclampsia without convulsions to total deliveries was 0.008 per cent.

### Case reports

**Case 1.** Mrs. A. J., a 45-year-old Negro woman, gravida xviii, para xiii, entered the Cook County Hospital on Nov. 16, 1945. The expected date of confinement was Jan. 4, 1946. She had had rheumatic heart disease with mitral stenosis and insufficiency. The blood pressure was 126/80, pulse 110, and respirations 34. The heart was enlarged to the left and a systolic murmur was heard at the apex. The uterus was enlarged beyond the expected stage of gestation. A diagnosis was made of rheumatic heart disease, Grade II, with mild decompensation, and possible asthmatic bronchitis.

The treatment was directed toward the apparent heart failure and consisted of aminophylline, parenteral Digalen, and oxygen. The patient pur-

sued a gradual but progressive downhill course and died on the ninth day after admission. At no time was there evidence of convulsions, coma, or hypertension.

**Essential pathologic findings.** The liver (1,760 grams) was moderately enlarged. Its surface was studded with hemorrhagic and necrotic foci. On cut surface the structure appeared to be well preserved. Microscopically, there was marked congestion in many of the lobules, primarily in the peripheral zone, where blood extravasations and focal necrotic areas were present. The kidneys weighed 330 grams together. Their surfaces were smooth and light yellow-red. Microscopically, the glomerular tufts were ischemic and the basement membranes were swollen. The heart (300 grams) was of normal size and configuration; the myocardium was firm. No evidence of recent or healed rheumatic valvulitis was found. A single large fetus (3,460 grams) was present in the uterus.

**Pathologic diagnosis.** The diagnosis was (1) hemorrhagic necrosis of the peripheral zones of the liver (eclampsia) and (2) acute membranous glomerulonephritis (eclampsia). (Tissue blocks or slides were unavailable from this case, which, however, was well documented.)

**Case 2.** Mrs. L. DeR., a 24-year-old white woman, gravida v, para ii, entered the Cook County Hospital on Jan. 28, 1948, in active labor at 21½ weeks' gestation. She had had eclampsia in 1943. Her abdomen had enlarged markedly in the 3 days before admission. The blood pressure was 110/70 and pulse 72. Fetal heart tones were not audible. Slight pitting edema of the extremities was present. The clinical impression was that of abruptio placenta. Simple amniotomy effected delivery of a small macerated fetus in 4 hours. The placenta, removed manually, was very large. Severe postpartum hemorrhage characterized her further course. This required two unsuccessful packings of the uterus, followed by a rapid supracervical hysterectomy, with transfusion of 500 c.c. plasma and 1,500 c.c. blood. At the time of operation, the uterus was boggy and there was marked subserous hemorrhage into the broad ligament. Her further clinical course was marked by an increasing oliguria from lower nephron nephrosis secondary to intra- and extrauterine bleeding. The nonprotein nitrogen determination finally rose to 125 mg. per cent. Preterminally, an attempt was made to create a makeshift artificial kidney. At no time did the patient have any con-

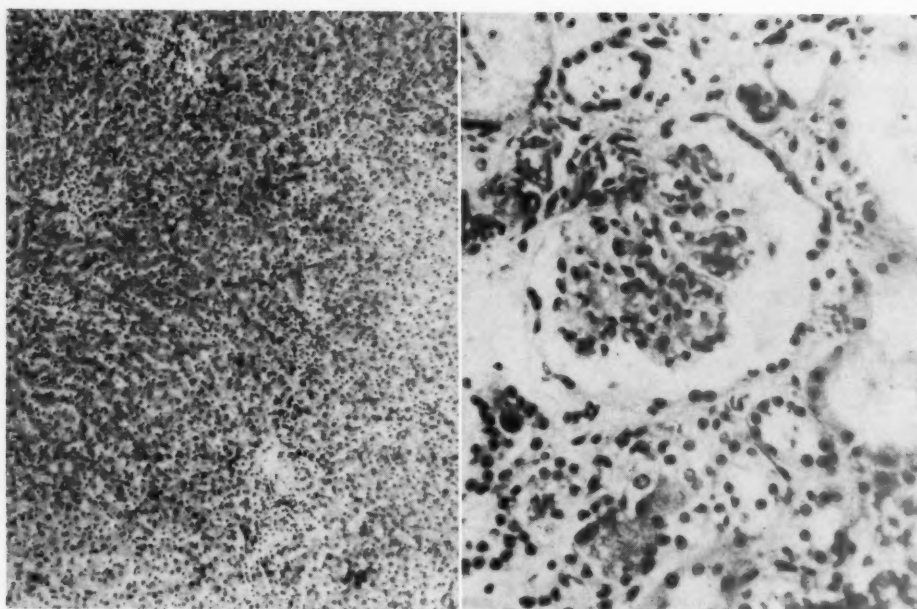


Fig. 1. Case 2. Liver; periportal fields moderately enlarged. Intralobular necrotic foci consisting of lymphocytes, polymorphonuclear leukocytes, and few eosinophils.

Fig. 2. Case 2. Kidney; slightly increased cellularity and mild thickening of the basement membrane of the capillary loops.

vulsions or reveal any hypertension. Blood pressure readings were within normal limits except for signs of shock after delivery and during hemorrhage. She died approximately 4 days after admission. During this time she received 4,000 c.c. of blood.

**Essential pathologic findings.** The liver (2,100 grams) was enlarged. The sinusoids were moderately congested, especially in the central zone. Scattered throughout the lobules, necrotic foci were seen, sometimes adjacent to the portal fields. The portal field itself was moderately enlarged and cellular and was infiltrated with lymphocytes, polymorphonuclear leukocytes, and eosinophils (Fig. 1). The necrotic foci, sometimes quite large, consisted of polymorphonuclear leukocytes, lymphocytes, and remnants of disintegrating liver cells. A few of the cholangioles contained olive green pigment casts. In some of the necrotic foci the sinusoids contained fibrin thrombi.

The kidneys (225 grams each) were large and had a pale, smooth surface. Microscopically, the glomeruli were moderately engorged with red blood cells. Bowman's spaces contained some eosinophilic granular material. There was a slight increase in the cellularity of the glomeruli due to endothelial proliferation and presence of

polymorphonuclear leukocytes. The basement membrane of the capillary loops was moderately thickened (Fig. 2). The proximal convoluted tubules contained fine granular material. The distal convoluted tubules, the loops of Henle, and the excretory ducts contained brown coarse granular material and showed various degrees of degenerative changes or disintegration. The interstitial connective tissue was loose and edematous. It showed foci of infiltration with lymphocytes, polymorphonuclear leukocytes, and eosinophils. This cellular infiltration was frequently perivenous.

In the brain (1,300 grams) the gyri were flattened and the sulci were narrowed. There was an extensive hemorrhage in the left gyrus cinguli. There were also numerous ecchymoses in the white substances of both cerebral hemispheres and the cerebellum, as well as in the corpus callosum and the right corpus subthalamic nuclei.

**Pathologic diagnosis.** Diagnosis was (1) cerebral hemorrhage; (2) lower nephron nephrosis; (3) pulmonary edema; (4) bilateral hydrothorax; (5) hydropericardium; and (6) focal necrosis of the liver.

**Comment.** This is a case of typical lower nephron nephrosis which developed subsequent to the postpartum bleeding and shock. However,

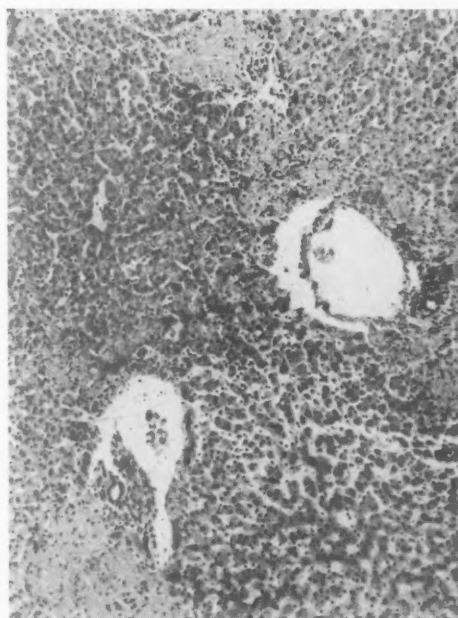
the cerebral changes, specifically the extensive hemorrhage in the left gyrus cinguli, cannot be explained as secondary to lower nephron nephrosis. Two possibilities have to be considered to explain the massive hemorrhage. These are (1) sickle cell crisis, and (2) eclampsia. Since it is known that a sickle cell crisis can be precipitated by shock and that it can cause cerebral hemorrhage, a careful search was made for any morphologic evidence of sicklemia. None was found. Eclampsia arising post partum could explain the cerebral hemorrhage. The hepatic pathology, characterized by extensive focal and periportal necrosis, is suggestive for eclampsia. The kidney (glomeruli specifically) did not reveal the pathognomic findings; however, the pathologic changes in the brain, in the absence of any other cause, would permit the assumption that the most likely cause was eclampsia.

**Case 3.** Mrs. E. J., a 29-year-old Negro woman, gravida vii, para iv, entered the Cook County Hospital on Nov. 14, 1947, at term with the diagnosis of pre-eclampsia characterized by headaches for one week, moderate ankle edema for one month, and hypertension of 170/90. Blood chemistry findings were normal, and slight to mild proteinuria was present. Treatment consisted of bed rest, sedation with morphine sulfate and chloral hydrate, sodium-poor diet, am-

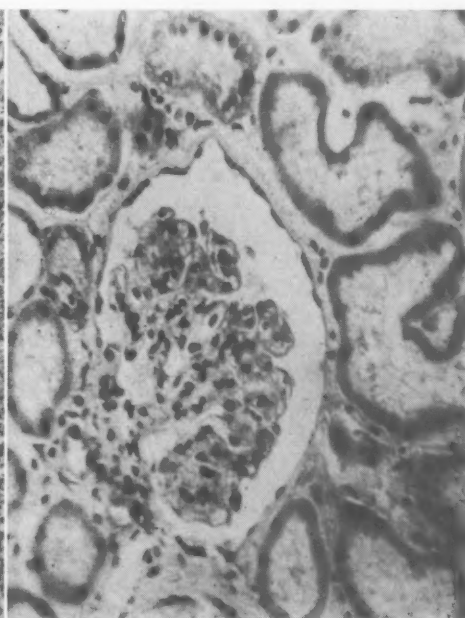
monium chloride, and intramuscular magnesium sulfate. She improved in 4 days with the blood pressure decreasing to 130/85. Attempted medical induction on the third day failed. Labor began spontaneously on the fifth day, at which time fetal heart tones had disappeared and the blood pressure had elevated to 200/124. After 4 hours she suddenly became seriously ill. The blood pressure was unobtainable and the pulse was weak. She had no remarkable complaints but died undelivered. A cardiovascular or intracerebral accident was postulated.

**Essential pathologic findings.** The uterus was enlarged to the xiphoid. There was a rent in the left anterolateral surface of the lower uterine segment measuring 9 by 6 cm. The myometrium was dissected by blood. The peritoneal cavity contained about 300 c.c. of dark brown liquid blood. The cervical os was dilated to 8 cm. The uterus contained a term male fetus. The placenta was completely normal and was implanted superoposteriorly.

The liver (1,800 grams) had a smooth surface mottled with small purplish areas. It was extremely friable. The cut surface bulged and showed pin-point hemorrhages. Microscopically, the sinusoids were congested. Scattered throughout the section, either in the midzone or in the peripheral zone of the lobules, small necrotic



**Fig. 3.** Case 3. Liver; clusters of necrotic liver cells in the peripheral zone of the lobule adjacent to the portal fields.



**Fig. 4.** Case 3. Kidney; slight thickening of the basement membrane of the capillary loops of the glomeruli.



foci were seen (Fig. 3). The sinusoids in these areas contained fibrin thrombi.

The kidneys each showed a small scar in the mid-polar region. Microscopically, Bowman's spaces of many glomeruli contained pinkish granular material. Many of the glomeruli were ischemic. The basement membranes of the capillary loops showed moderate thickening (Fig. 4). There was also a slight increase in the cellularity of the glomeruli chiefly due to proliferation of the endothelial cells. The arterioles were slightly thickened. The lumina of the proximal convoluted tubules contained eosinophilic granular material.

**Pathologic diagnosis.** The diagnosis was (1) rupture of the uterus; (2) hemorrhagic zonal necrosis of the liver (eclampsia); (3) moderate acute membranous glomerulonephritis; (4) edema of the brain; and (5) dilatation of the left ventricle.

**Case 4.** Mrs. J. S., a 30-year-old white woman, gravida iv, para iii, entered the Cook County Hospital on Sept. 11, 1949, at 37 weeks' gestation in active labor with breech presentation, one leg having already delivered. Her prenatal course had been normal until 10 days prior to admission when 2-plus proteinuria was found. A living female infant, 4¾ pounds, was soon de-

livered. Shortly thereafter, the patient was noted to be cold and clammy. The blood pressure was 200/120. The uterus was explored internally for possible rupture, but none was found. The catheterized urine coagulated solidly with its precipitated protein.

Treatment consisted of moderately heavy sedation and 25 per cent glucose given intravenously. The patient rested quite comfortably thereafter for the next 6 hours with only a slight drop in blood pressure. About 9 hours after admission she suddenly went into shock and died within one hour in spite of various cardiac stimulative efforts.

**Essential pathologic findings.** There were numerous petechial and confluent hemorrhages in the subcapsular areas. Microscopically, the lobular pattern was preserved in some areas, with fibrin thrombi in the sinuses and periportal hemorrhagic necrosis. In other areas the lobular pattern was obscured or destroyed because of extensive hemorrhage involving entire lobules (Fig. 5). Microscopically, many of the glomeruli of the kidneys (500 grams together) were seen to be enlarged and ischemic. The basement membranes of the capillary loops appeared definitely thickened. Moderate increase in the intracapillary cellularity due to proliferation of the endo-

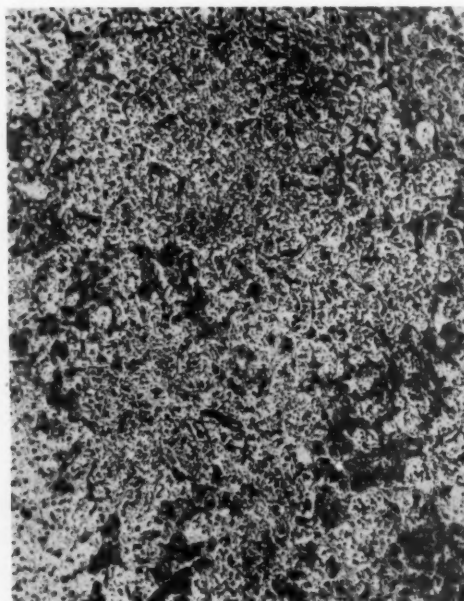


Fig. 5. Case 4. Liver; hemorrhagic necrosis chiefly in the peripheral zone of the lobule.

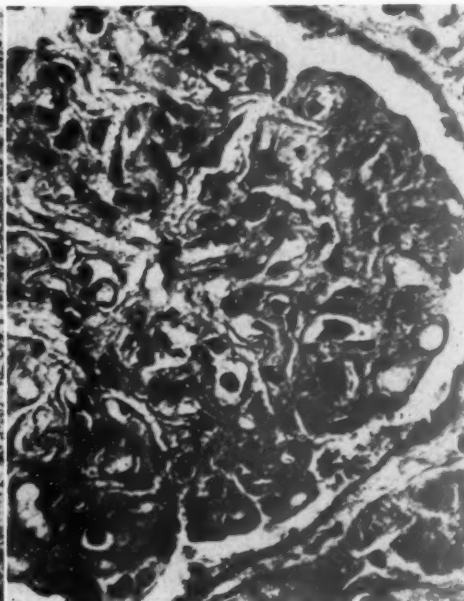


Fig. 6. Case 4. Kidney; thickened basement mem-

brane of the capillary loops and moderately increased intracapillary cellularity due to proliferation of the endothelial cells.

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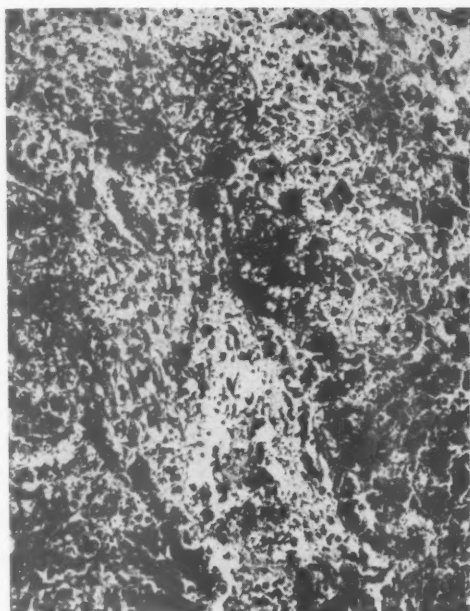


Fig. 7. Case 5. Liver; hemorrhagic intralobular necrosis chiefly adjacent to the portal fields.

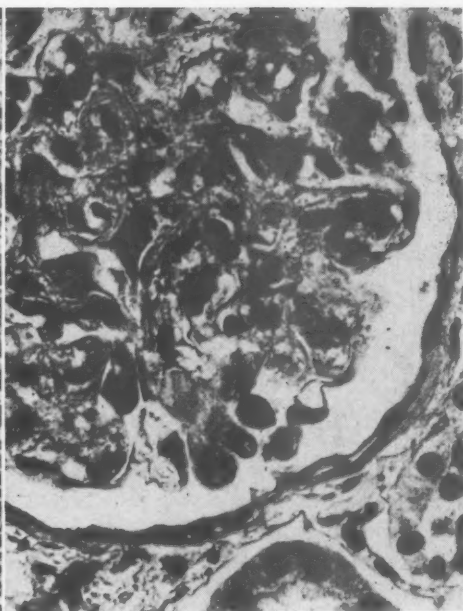


Fig. 8. Case 5. Kidney; prominent endothelial cells in the glomerular loops.

thelial cells was also seen (Fig. 6). The lining epithelial cells of the proximal convoluted tubules were swollen. The arterioles were thickened.

*Pathologic diagnosis.* The diagnosis was (1) hemorrhagic necrosis of the liver (eclampsia); (2) acute membranous glomerulonephritis; and (3) dilatation of all cardiac chambers.

**Case 5.** Miss L. M., a 15-year-old Negro girl, gravida i, para 0, entered the Cook County Hospital on Oct. 25, 1951, at about 28 weeks' gestation. Her blood pressure was 200/120. Edema of the upper eyelids, legs, and ankles was moderately severe. The fundi showed constricted arterioles, localized spasm, and perivascular edema. Laboratory findings revealed proteinuria 4 plus, hemoglobin 84 per cent, nonprotein nitrogen 48 mg. per cent, total protein 4.8 mg. per cent, serum albumin 2.8 mg. per cent, and uric acid 11.4 mg. per cent. Treatment consisted of sedation, bed rest, ammonium chloride, salt-poor diet, and hypertonic glucose intravenously. She improved for several days with the blood pressure stabilizing at 155/110. An intravenous veratrum viside compound given twice gave little benefit. Further clinical improvement was not obtained; on the twelfth day a laparotrachelotomy under spinal anesthesia resulted in the delivery of a living  $3\frac{3}{4}$  pound baby. Several hours after operation, the patient went into shock but responded to

stimulants. During the first 24 hours after operation only 45 c.c. of bloody urine was obtained. Sternal marrow puncture gave the picture of thrombocytopenic purpura, thought to be on a toxic basis. The patient was bleeding from the gums. In spite of the administration of blood (1,300 c.c.), plasma (500 c.c.), and ACTH (10 mg.), she died 36 hours after operation.

*Essential pathologic findings.* The consistency of the enlarged liver (1,900 grams) was decreased. Microscopically, foci of hemorrhagic necrosis were seen chiefly about the peripheral zones of the lobules, and fibrin thrombi were present in the sinuses (Fig. 7). The kidneys (440 grams together) on cut section revealed hyperemia along the corticomedullary line. Microscopically, the glomeruli were ischemic. Bowman's spaces contained pinkish eosinophilic coarse granular material. The basement membranes of the capillary loops were swollen. The endothelial cells were prominent (Fig. 8). The proximal convoluted tubules contained some granular material. Many of the distal convoluted tubules contained brown granular casts. The interstitial connective tissue was loose and somewhat edematous and contained occasional lymphocytic foci.

*Pathologic diagnosis.* The diagnosis was (1) hemorrhagic necrosis in the peripheral zone of

the liver lobules (eclampsia); (2) acute membranous glomerulonephritis; (3) early lower nephron nephrosis; (4) edema of the brain; (5) dilatation of all cardiac chambers; and (6) essential thrombocytopenia (hematologically).

**Case 6.** Mrs. T. G., a 30-year-old Negro woman, gravida i, para 0, entered the Cook County Hospital on Feb. 11, 1954, at 20½ weeks' gestation, complaining of dyspnea and severe epigastric pain. The blood pressure was 250/110. The abdomen was so extremely tender below the xiphoid that other acute abdominal conditions were simulated. Slight pretibial edema was present. The ocular fundi showed spasm. The urine revealed 4-plus protein and profuse numbers of tubular casts and erythrocytes. The blood showed a hematocrit count of 27, normal platelet and differential counts, clotting time of 8 minutes, nonprotein nitrogen 57 mg. per cent, and uric acid 11.8 mg. per cent. Therapy consisted of sedation, magnesium sulfate, and intravenous hypertonic glucose. In the absence of improvement and since the patient had no tremors or convulsions, an abdominal hysterotomy was performed under local anesthesia on the second day and resulted in the delivery of a living fetus of 20 weeks' size that died shortly. Blood loss during the operation was about 300 c.c. The placenta showed fibrosis and calcifications. Post-operatively, the patient exhibited tachycardia and hyperpnea. In spite of the administration of digitalis, intravenous dextran, and, later, 50 per cent dextrose, she died 24 hours after operation.

**Essential pathologic findings.** The liver (1,200 grams) showed punctate hemorrhages and pinpoint yellowish areas. Microscopically, the sinusoids were congested, especially around the central vein. In the peripheral zone the liver cells showed eosinophilic necrosis. The portal fields were moderately enlarged and infiltrated by polymorphonuclear leukocytes. Many of the sinusoids around the portal fields contained fibrin thrombi. In some of the lobules, especially subcapsularly, the necrosis was more extensive, involving also the midzone and occasionally the entire lobule. The kidneys (200 grams together) had widened cortices. Microscopically, the glomeruli were ischemic. Bowman's spaces were narrowed, many of them containing eosinophilic material. The basement membrane of the capillary loops was swollen (Fig. 9). The afferent arteriole showed some thickening. The proximal convoluted tubules were lined by swollen epi-

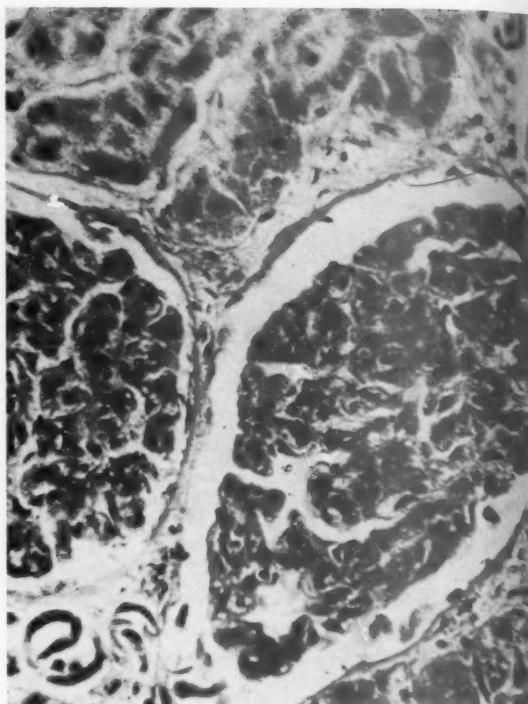


Fig. 9. Case 6. Kidney; thickened basement membrane of the capillary loops of the glomerulus.

thelial cells. The distal convoluted tubules contained red blood cells or pigment casts. The interstitial connective tissue was loose and edematous.

**Pathologic diagnosis.** The diagnosis was (1) zonal (peripheral) sublobular and lobular necrosis of the liver (eclampsia); (2) acute membranous glomerulonephritis; (3) lower nephron nephrosis; (4) pulmonary edema; and (5) fibrinous pericarditis.

**Case 7.** Mrs. B. B., a 28-year-old Negro woman, gravida ii, para i, entered the Cook County Hospital on Dec. 2, 1954, at 15 weeks' gestation with a blood pressure of 226/140. The child born 11 years before, after a normal pregnancy without hypertension, had died. The patient's heart was moderately enlarged. The urine, containing to 1-plus protein, concentrated to 1.020 and diluted to 1.005. In spite of active sedative therapy there was no improvement but therapeutic abortion was repeatedly refused. On final readmission, after several signed releases, the blood pressure was 240/140, proteinuria was 4 plus, and total urinary protein output was 6.1 Gm. The active fetus had not grown in a month. The patient finally agreed to a hysterotomy under local anesthesia on Feb. 1, 1955. The ab-

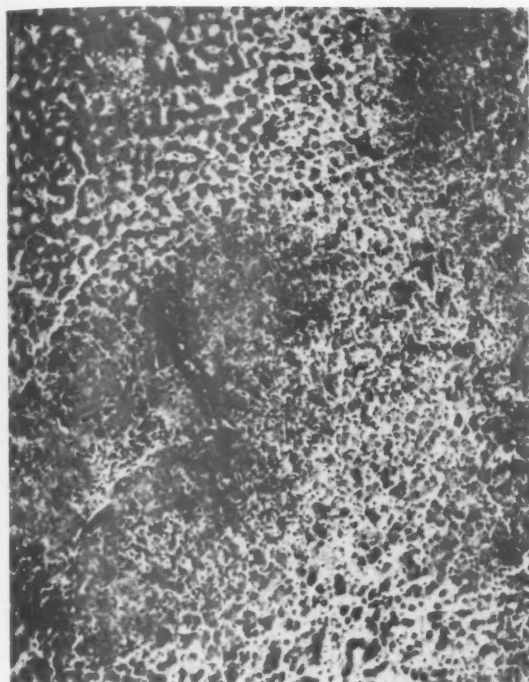


Fig. 10. Case 7. Liver; severe intralobular necrosis.

dominal and uterine wounds were dry upon completion of the operation. Postoperatively, in spite of several blood transfusions and Levophed, she lapsed into shock. Intra-abdominal bleeding was not detected until preterminally. Then, absence of clotting after 40 minutes was noted. The prothrombin time was 75 seconds, platelets were decreased, fibrinolysin was strongly positive in 1:128, fibrinogenolysin was also strongly positive, and fibrinogen was zero. Five grams of intravenous fibrinogen had no favorable effect. She had received 11 pints of blood but died 12 hours postoperatively.

**Essential pathologic findings.** The peritoneal cavity contained about 300 c.c. of dark brown liquid blood. The rectus abdominus muscle and the subcutaneous tissue over the recent wound was partly infiltrated with blood. Numerous scattered petechial hemorrhages were present over the epicardium. The liver (1,625 grams) had numerous subcapsular hemorrhages. Microscopically, the portal fields were enlarged owing to edema and moderate infiltration with lymphocytes and polymorphonuclear leukocytes. The peripheral zones of some of the lobules showed necrosis, hemorrhage, and fibrin thrombi in the sinusoids (Fig. 10).

The kidneys (275 grams together) had uniformly granular surfaces, "flea-bite" hemorrhages, and narrowed cortices. Microscopically, many of the glomeruli were engorged with red blood cells and were occasionally enlarged and cellular, chiefly because of proliferation of the perithelial cells. Occasionally the glomerulus showed adhesions with the parietal layer of Bowman's capsule. The arterioles and small arteries were thickened, appeared distinctly smudgy, and showed intimal proliferation with onion-like thickenings and narrowing of the lumina. The lining epithelium of the proximal convoluted tubules was swollen, granular, and eosinophilic. The distal convoluted tubules, those of the loops of Henle, and occasionally the excretory ducts showed deposits of calcium. The interstitial connective tissue was infiltrated with lymphocytes and occasionally with polymorphonuclear leukocytes. This infiltration was chiefly peritubular. Some of the tubules of the lower nephron and the excretory ducts contained polymorphonuclear leukocytes. The brain (1,400 grams) showed flattening of the gyri and occasional petechiae in the white matter.

**Pathologic diagnosis.** The diagnosis was (1) malignant nephrosclerosis; (2) zonal lobular necrosis of the liver (eclampsia); (3) edema of the brain; (4) edema of the lungs; and (5) hemorrhagic diathesis due to afibrinogenemia.

### Comment

The main aspect of this discussion is concerned with the pathologic lesions seen in eclampsia.

**Liver lesions.** According to Sheehan,<sup>4</sup> in the majority of the livers in patients having convulsive toxemia, only a few petechial hemorrhages are on the surface and, on cut section, these lesions usually cannot be identified. In severe cases, however, numerous petechiae can be seen beneath the capsule, and on cut section the lesions resemble a recent venous congestion. In very severe cases, the diffuse hemorrhages are visible. Microscopic examination may show numerous periportal hemorrhages, or there may be so few that several slides must be examined to find a single focal lesion. In his opinion, these lesions are not specific for eclampsia, but may also be seen in abruptio placentae, in malignant hypertension associated with



cerebral hemorrhage, and in sudden and unexplained deaths of patients in labor who may have had fulminating eclampsia. He believes that the majority of liver lesions in fatal eclampsia occurred during the last day of life and are not produced by the convulsions per se, since they occur in eclampsia without convulsions.

In 1946, Ingerslev and Teilum,<sup>10</sup> from liver biopsy studies, found that characteristic microscopic changes occurred only in an occasional case of pronounced late toxemia, and in more than half of those patients with eclampsia. These changes included periportal precipitation of fibrin with necrosis and hemorrhage. Dieckmann<sup>8</sup> obtained liver tissue by needle biopsy from a patient with pyelonephritis and convulsive toxemia in which there was evidence of subcapsular hemorrhage, but the liver was histologically normal. Twelve other patients with eclampsia were subjected to direct liver biopsy at the time of cesarean section but showed no subcapsular hemorrhage. He believes that there is no pathognomonic liver lesion in eclampsia.

No needle biopsies were made of the liver in any of the cases included in this study. However, one of the few attempted was on a patient with acute fulminating toxemia about 20 hours after a convulsion and just prior to the performance of cesarean section. The results of this biopsy are seen in Fig. 11, which shows the typical liver changes in eclampsia. Waldstein and Szanto,<sup>11</sup> investigating the accuracy of the liver punch biopsy in depicting the true condition of the liver found that it was truly representative. The diseases they studied, however, had a more generalized distribution throughout the parenchyma of the liver than does eclampsia where the pathologic lesions are not always diffuse but are frequently focal. Perhaps further liver biopsy studies may eventually help to establish a proper relationship in this matter.

In our 7 cases, the liver lesions were fairly characteristic of the criteria set down by Sheehan. The findings were surprising in Case 1, however, since this patient died of

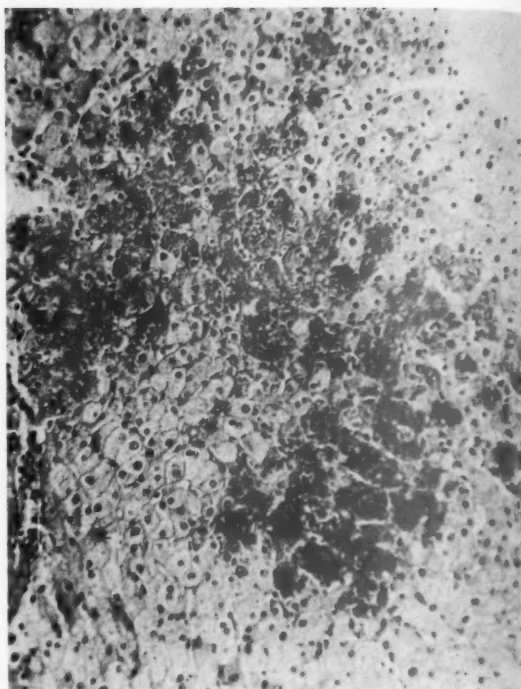


Fig. 11. Liver biopsy; foci of hemorrhagic intra-lobular necrosis.

apparent cardiac decompensation with normal blood pressure, urinary findings, and blood chemistry determinations. Only on the basis of the pathologic findings of macroscopic liver hemorrhages, mild periportal cell necrosis, and swollen glomeruli with thickening of the basement membrane, could this patient be considered as having "eclampsia without convulsions." Dieckmann's probable contention would be that this patient may have developed these lesions preterminally in the last 48 hours, and this merits consideration.

**Kidney lesions.** A variety of descriptions of typical kidney lesions in eclampsia are present in the literature. Fahr<sup>12</sup> has stated that "microscopically, the glomeruli are enlarged with thickening and swelling of the basement membrane of varying intensity. The glomeruli are ischemic. Lipid deposits are present in the glomeruli and more so in the tubular epithelium. All these changes may occur in cases of eclampsia without convulsions." According to Sheehan,<sup>4</sup> the thickening of the basement membrane is the



result of a "nonspecific staining technic." The lesions of the glomerulus could develop in one or two days and become histologically normal within one week after clinical recovery. In older multiparous patients these lesions are more severe and striking. Some protein casts and hyaline droplets may occur in the proximal convoluted tubules. Sheehan believes that the kidney lesions bear a definite relationship to the degree of blood loss and duration of shock which, in turn, may have caused arterial spasm of the renal arteries for varying periods of time. This may also lead to lower nephron nephrosis.

Pollak and associates<sup>13</sup> performed kidney needle biopsies on 15 women with pre-eclamptic symptoms during the height of the disease process and on 9 of these women in the postpartum period after the toxic phase had receded. They consistently found a thickened glomerular basement membrane, and proteinaceous material often present in Bowman's spaces and in the lumina of the convoluted tubules. The postpartum biopsies revealed normal kidney histology, except for one patient in whom hypertension persisted.

In our 7 cases, pronounced ischemia of the glomeruli was present in Cases 1 and 6, and thickening of the glomerular tuft was present in 6 of the 7 cases. This latter was partly due to swelling of the endothelial cells but, to a greater extent, to a thickening of the basement membrane, as noted in 5 instances. In those cases in which the McManus periodic acid-Schiff (PAS) staining technique was employed (Cases 5 and 7), the thickening of the basement membrane appeared to be due to a deposit of PAS-positive material.

There is some controversy about the nature of the thickening of the basement membrane of the endothelial cells in the glomerular tuft. According to Sheehan,<sup>4</sup> it is due to a staining artifact; according to Pollak,<sup>13</sup> it is due to an edematous swelling and not to a deposit of mucopolysaccharide material; Dieckmann and McCartney,<sup>14</sup> on the basis of their biopsy material, believed that some change takes place to cause a

specific histochemical staining reaction, but whether this is due to a deposition of a polysaccharide or to edema alone they cannot say.

Necrobiotic changes in the proximal convoluted tubules were present in Cases 1 and 4. In addition, lower nephron nephrosis, as a terminal episode, was found in 4 of the 7 cases. Other kidney lesions seen included old pyelonephritis and hydronephrosis in Case 3 and severe nephrosclerosis and glomerulonephritis in Case 7.

**Brain lesions.** The lesions in the brain of eclamptic patients vary. Many have no gross lesions. Most strikingly there is frequently microscopic cerebral hemorrhages, softening, or meningeal hemorrhages. Sheehan<sup>4</sup> states that about one third of the cerebral hemorrhages are macroscopic, and two thirds are only microscopic. He further believes that the lesions that cause postpartum eclampsia are due to cerebral venous thrombosis. In our series of cases, brain changes were seen in Case 2, which manifested multiple hemorrhages throughout, and in Case 7, which showed a small amount of hemorrhage in the white matter of the brain stem. The absence of more severe morphologic alterations in our cases of eclampsia without convulsions may be due to the absence of spasm, paralysis and thrombosis of the blood vessels, as compared with those cases with convulsions. Josephy and Hirsch,<sup>15</sup> after observation of a patient who died with severe brain destruction 3 months after eclampsia with severe convulsions, believed that these changes occur more frequently than have been reported and that patients with less extensive destruction may have clinical symptoms which are inconspicuous and which are overlooked.

**Etiology of convulsions.** The exact cause of convulsions in eclampsia is not known. In the past, convulsions were considered a necessary feature of eclampsia. However, authors such as Macintosh<sup>16</sup> believe that seizures in a patient with cerebral dysrhythmia are "merely a reflection on the patient's epileptic diathesis rather than being due to the severity of the toxemia precipitat-

ing the seizure. A more stable personality is more resistant and will convulse only when the stimulus is more intense." In some women the cortical discharges are so inherently stable that toxemia of pregnancy can reach the extreme degree where the patient dies with severe eclamptic pathologic changes without any suggestion of twitchings or fits. Of 19 patients who died from toxemia of pregnancy, he observed 8 who had no convulsions. He believed that the occurrence of fits in a pregnant woman gives no indication of the gravity of that particular case.

The suggestion that eclampsia is only a partial manifestation of epilepsy is not a new one. Feré, the French psychiatrist, suggested the relationship 70 years ago (1890). The external features of eclamptic fits do not differ from those of fits due to many other causes. Rosenbaum and Maltby,<sup>17</sup> investigating the electroencephalographs of patients with toxemia of pregnancy, found that of 20 patients with convulsions 13 had cerebral dysrhythmia and a family history of convulsions. Of 20 patients without convulsions only 2 had cerebral dysrhythmia and 2 had a family history of convulsions. They conclude that eclampsia occurs more readily in patients with a constitutional predisposition to convulsions. Brown<sup>18</sup> believed that cerebral dysrhythmia is such an important factor that "if fits were to supervene in the presence of severe pre-eclampsia, it would be difficult to decide whether they were epileptic fits in a pre-eclamptic or eclamptic fits in an epileptic."

The exact cause of convulsions, in spite of these studies, is not known. In view of the intense pathologic changes noted in our patients, one may speculate that the occurrence of convulsions might have served a useful function to alert us to more definitive therapy sooner. As an "alarm" system, convulsions could be considered as invaluable. It is when these convulsions are absent that we must keep in mind the "severity" of the toxic state of the patient in order to avoid a fatal outcome. A better appreciation of

the "severity" will call forth decisive action more quickly. Thus, the absence of convulsions can, paradoxically, at times be a disservice to the patient by giving the obstetrician a false sense of security.

### Summary and conclusions

1. Seven cases of so-called "eclampsia without convulsions" are presented. The entity occurs about once in every 12,670 deliveries, an incidence of 0.008 per cent, in a busy charity maternity service. Eclampsia with convulsions occurred once in every 452 deliveries, an incidence of 0.2 per cent. The ratio between these two types of eclampsia was thus 1:28.

2. The pathologic criteria which establish the diagnosis of eclampsia are discussed. The occurrence of these criteria in cases where they are "surprise" findings, i.e., without clinical pre-eclampsia, makes one wonder whether these criteria can be justifiably maintained.

3. Further liver and kidney biopsy studies may eventually help to establish a relationship between the pathologic lesion and the clinical entity.

4. The relationship between convulsions and cerebral dysrhythmia is alluded to once again. One is reminded that convulsive seizures, even in the presence of toxemia, do not necessarily make a diagnosis of "eclampsia."

5. The degree of severity of some of the pathologic changes seen in several of the cases where clinical "pre-eclampsia" was present, emphasizes the fact that convulsions serve a beneficial function in calling forth decisive action quickly. It also reminds us of the necessity for decisive action in many cases though convulsions do not, or will not, occur.

6. Since definitive treatment is often delayed by a conservative therapeutic attitude whenever a diagnosis of "pre-eclampsia" is made, a more careful evaluation and appreciation of the "severity" of the condition is necessary to avoid a fatal outcome, even though convulsions have not yet occurred.

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# Discussion

DR. EDWIN F. HIRSCH, Chicago, Illinois. The foci of necrosis in the liver of the patient dying of eclampsia commonly involve the periphery of the lobules. Some livers which seem only slightly damaged grossly display microscopically lesions that are both extensive and severe.

The kidneys have acute and chronic changes, the latter mainly occlusions of the arteries. The tissue changes in the kidneys in eclampsia must be carefully evaluated so as not to include some antecedent and unrelated disease. Eclampsia seems to be a profound metabolic disorder with severe injury and hemorrhage of the liver parenchyma and similar changes of the kidneys and secondary thrombosis.

DR. WILLIAM J. DIECKMANN.<sup>†</sup> Some years ago at a meeting of the Chicago Maternal Mortality Committee, we reviewed two deaths in the same year in patients who had periportal hemorrhage and necrosis, the so-called hepatic lesion of eclampsia. A deputy coroner who was a member of the committee stated that both of the cases should have been coroner's cases, but he assumed that because the woman was pregnant the doctor considered the death due to a complication of pregnancy.

The first thought of any physician who is treating a pregnant woman having convulsions and/or coma is that these are due to eclampsia.

During the past 25 years, however, it has become evident that many other conditions can be the cause of these symptoms, as evidenced by the following list in which the convulsions and/or coma have been due to other diseases than eclampsia: hypertensive encephalopathy, uremia (due to acute or chronic glomerulonephritis, extensive kidney destruction from pyelonephritis, or nephrosclerosis), anesthesia (nitrous oxide, cyclopropane, ethylene), hysteria, epilepsy, alkalosis, accident, shock, diabetes mellitus, hypoglycemia (overdosage of insulin), brain tumors, meningitis, localized brain abscess, poisoning (cocaine, lysol, alcohol), scleroderma, porphyria, leukemia, and coronary thrombosis. It must always be kept in mind that there is nothing characteristic about the convulsion or the coma which occur in true eclampsia. They are merely the symptoms of a cerebral disturbance which may be due to anoxia, edema, hemorrhages of all sizes, or arteriolar spasms.

A study of autopsy material, liver biopsies, and inspection of the liver in toxemic patients after cesarean section convinced me some years ago that the periportal hemorrhage and necrosis are not pathognomonic of eclampsia. This lesion means that the patient is pregnant or is in the very early puerperium. The lesion is dependent primarily on circulatory changes in the liver, i.e., hemoconcentration associated with either hyper- or hypotension and a decrease in the clotting time of the blood in the liver.

The kidney lesion, namely, the enlarged glo-

<sup>†</sup>Died Aug. 15, 1957.

merulus, has been described as being characteristic of eclampsia, but since it is extremely rare for a pre-eclamptic patient to die, no one knew what the lesion was in that condition. Bell, Sheehan, and McManus, in reviewing our biopsies of normal pregnant patients and patients with hypertensive disease, pre-eclampsia, and eclampsia, noted that the typical changes which they thought were characteristic of eclampsia were found with greater frequency and in a more marked degree in pre-eclamptic patients. One of our eclamptic patients had a minimal lesion, while the most marked glomerular change was noted in a primipara who had only proteinuria late in pregnancy, lasting for about 5 days. This glomerular lesion is a reversible one and has disappeared by 6 months post partum without any histological or physiological evidence of any permanent damage.

The authors have collected 7 fatal cases: a cardiac patient, a hypertensive patient, 2 patients in shock (one from a ruptured uterus and the other from an unknown cause), a patient with so-called purpura which may have been the end result of a toxemia, and a woman who had gone through 13 pregnancies.

Four of their patients were over 30 years of age and yet statistics indicate that eclampsia is a disease of young women. Five were multiparas, and yet eclampsia is a disease of primi-

parity. Three had a gestation of less than 25 weeks' duration, and yet eclampsia is a disease primarily of the last trimester.

Our studies indicate that pre-eclampsia-eclampsia—and we think the two differ only in the fact that convulsions and/or coma occur in the latter—is a reversible disease until almost the time of death, provided the patient is properly treated. If the patient is having no convulsions, do not give her sedatives. If she is not excreting urine, do not give 5 per cent dextrose solution, for it will *not* work and will only overload her circulation. Give small amounts, 100 to 200 ml. of 50 per cent or 30 per cent, or larger amounts of 20 per cent, dextrose intravenously. The patient must lose weight if she is to survive. Most important, do not wait too long to terminate the pregnancy; this should be done preferably by the vaginal route if delivery can be anticipated within less than 24 hours. These patients do not stand labor well because of the circulatory changes in blood and fluid compartments. There is no objection to cesarean section, preferably under local anesthesia, provided the doctor's over-all maternal mortality rate in cesarean section is less than 0.2 per cent. These patients are poor operative risks. The treatment must be continued after delivery until the normal diuresis sets in, usually within 24 to 48 hours after delivery.



# Comparison of intravenous saccharated iron oxide and whole blood in treatment of hypochromic anemia of pregnancy

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THE prevalence of anemia in the pregnant woman has been known since 1842, when first described by Channing.<sup>3</sup> Since that time innumerable investigations have been undertaken on the subject, some describing new methods of therapy, while others approach it from the standpoint of diagnosis, iron metabolism, or new methods of study.

The present paper is intended as a general review and is an attempt to compare the results in two of the more common methods of treatment; viz., intravenous saccharated iron oxide and direct blood transfusion.

It has been well established<sup>1, 2, 4, 6, 8</sup> that most anemias of pregnancy are hypochromic and result from an iron deficiency. The multiplicity of names for various anemias and the confusion that arises each time a new name or variation is added is well known. Like Hamilton and his associates,<sup>6, 7</sup> we believe the best present classification of anemias in pregnancy to be that set forth by Holly<sup>8</sup> wherein all anemias are classified into two main groups:

## A. Anemias directly related to pregnancy:

1. Iron deficiency anemia in pregnancy.
2. Megaloblastic anemia in pregnancy.
3. Hypoplastic anemia in pregnancy.

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## B. Anemias not directly related to pregnancy:

1. Sickle cell anemia.
2. Hemolytic anemia.
3. Anemia of infection, etc.

With one exception, all the cases in the present study are discussed under the heading of iron deficiency anemia in pregnancy (A-1). The single exception proved to be a case of Cooley's anemia which was treated with good response by intravenous iron injections.

## Metabolism of iron

The total amount of elemental iron in the body has been variously estimated as between 3.0 and 5.0 Gm. and is probably actually about 4.0 Gm. in the average nonpregnant woman. Iron itself is an unusual element in that there is virtually no excretion from the body, and the iron in the body is utilized over and over again. As such it becomes an essential constituent of hemoglobin, being responsible for the oxygen-carrying power of this molecule. However, it is also vital for the chemical make-up of certain enzymes, notably the cytochromes, catalase, peroxidase and cytochrome oxidase.

The *absorption* of iron is governed by many factors, and any factor which will decrease the absorption of iron can indirectly decrease the hemoglobin formation and the

total iron content of the body. Absorption is most efficient when the iron is reduced to the ferrous ion and thus any factor which affects this reduction may influence absorption. An increased alkalinity of the intestinal tract, a decrease in the hydrochloric acid formation of the stomach, or an excess of bile acids with production of insoluble iron salts may therefore play a significant role in absorption. Even though the iron may be in the ferrous form, an increase in the intestinal motility may allow for too rapid passage of the element for proper assimilation.

Iron itself, regardless of the form in which it is ingested, is absorbed in relatively minute amounts. This assimilation is governed by a rather remarkable chemical arrangement. The gastric juices first reduce the iron to a ferrous form, probably catalyzed by the presence of ascorbic acid. The rate of absorption is then regulated by the needs of the organism, the need being higher in anemia. In the

cells of the intestinal epithelium is a protein molecule, *apoferritin*, which is regarded as a protein with which the ferrous ion readily combines to form *ferritin*, an iron-protein complex. Ferritin is generally regarded as the storage form of iron and is found in the liver, spleen, and bone marrow. It is believed that there is an equilibrium set up within the intestinal epithelial cells themselves between the ferrous ion and the ferritin which contains iron in the ferric form.

The circulating form of elemental iron is in the plasma, and this quantity is almost insignificant in amount but is vital to the maintenance of balance and the ability to call forth greater or lesser absorption, its level being directly controlled by the needs of the body. It is believed that as long as there is an adequate store of ferritin there is an adequate store of ferrous ion, and this in turn will block the absorption of any further iron.

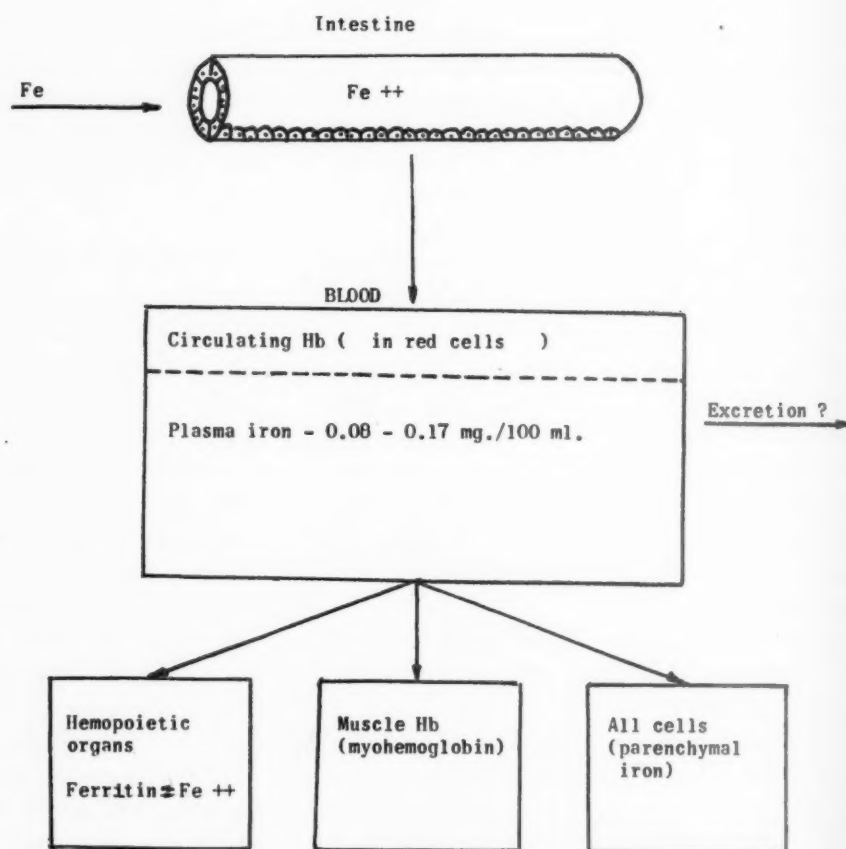


Fig. 1. Schematic diagram of iron metabolism.

Once iron is absorbed into the circulation as ferrous ion, it automatically oxidizes to ferric ion and becomes distributed to various tissues, primarily the hemopoietic organs (liver, spleen, and bone marrow) where it is stored as ferritin. Ferritin can in turn readily be reduced to liberate the ferrous ion; this then can be introduced into the heme molecule to form hemoglobin. This hemoglobin synthesis goes on daily, with approximately 7 to 8 Gm. of hemoglobin being destroyed daily and regenerated at the same rate. Not all iron is distributed to the hemopoietic tissues alone. The substance may also be deposited in muscle as *myohemoglobin*, which likewise undergoes constant resynthesis. Some iron may be used as the functional iron of tissues, such as that in cytochrome oxidase where the iron atom is necessary for the functional activity of the cell. Such iron is called *parenchymal* or *functional iron* and is found in all cells of the body.

Thus, 65 per cent of the body iron is found in hemoglobin, 20 per cent in the storage form of myohemoglobin, and 15 per cent as functional iron. Fig. 1 schematically depicts the cycle of iron metabolism.

The *excretion* of iron is almost nil. Excretion in the urine amounts to approximately 1.0 mg. of iron per day, and excretion by other means is almost nonexistent. That excreted in the feces is not true excretion, but rather an "overflow" from amounts ingested in food and never really absorbed. Thus, if the iron content of the body cannot be regulated by excretion, it must be regulated by the needs and absorption of the organism.

#### Present methods of iron replacement

At the present time there are four general methods of replacement of iron in the pregnant anemic woman. These may be used singly or in combination, and there is frequently an overlapping of one or more forms of therapy as each case is individualized. However, a brief discussion of each method will serve to form a basis for consideration of the therapy undertaken in the present report.

*Oral administration* of iron as one of its ferrous salts is perhaps the most frequently

utilized method of correction of hypochromic anemia. This is a tried and reliable method<sup>10</sup> and is one which has the advantage of being economically feasible for the patient and which may be carried out on an ambulatory basis without the necessity of painful injections. Other than occasional mild intestinal symptoms, particularly constipation, there are relatively few side effects. The oral form of administration requires a prolonged period of therapy, however, and approximately 3 months of treatment is needed before an adequate hemoglobin level can be obtained. Such a period of time is frequently not available in the pregnant patient, where a definite time limit is set by the estimated date of delivery. There is also the possibility of poor absorption because of "mucosal block" or any upset in the previously mentioned factors that govern absorption.

*Intramuscular administration* of iron has recently become popular in this country, having been used in Europe for several years prior to its introduction here. Iron of this type is available as an iron-dextran complex and has been proved to be equivalent to intravenous iron in its ability to correct anemia.<sup>5, 11</sup> Although the side effects have been reported as less severe and less frequent than those seen with intravenous forms of iron, the amount that can be given per dose without production of annoying local irritation is less. We have also noted several cases treated with intramuscular iron in which the patient has been left with a permanent local pigmentation because of too shallow or too direct an injection.

*Intravenous iron* is the third method of supplying iron to the patient with hypochromic anemia. This, too, is a well-established method of replacement and, like the other forms of therapy, has both advantages and disadvantages. One advantage is a rapid response in hemoglobin production since the elemental iron is deposited directly into the blood stream and no absorption is necessary. Hematologic response usually occurs within 2 weeks. Disadvantages are those of the side effects that may arise. These are usually mild but occasionally may be quite severe.

The fourth method of replacement in the pregnant woman is that of *direct blood transfusion*. This is a mode of treatment which has all the advantages that only replacement of whole blood can offer. However, the misfortunes that may arise with incorrect cross matching or the transfusion reactions that may occur even with expert laboratory facilities make one cautious about the indiscriminate use of whole blood. A more practical objection is the always difficult problem of replacement to the blood bank by sufficient and suitable donors.

The preceding review of iron metabolism and the discussion of methods of iron replacement is admittedly elemental in nature, but we believe it will allow an adequate basis for understanding the methods of therapy we have undertaken in this study. For the interested reader who may wish to pursue the topics further, the excellent text of Wintrobe<sup>12</sup> will furnish an exhaustive study of all aspects of hypochromic anemia in pregnancy, iron metabolism, and methods of therapy. The text of Mollison<sup>13</sup> is also highly recommended, particularly with regard to the administration of whole blood.

#### Methods and materials

Because of the possibility of reactions to whole blood and the difficulty of obtaining it, the authors began the present study to determine the efficacy of another method of replacement. Since it had long been the custom in this hospital to correct all anemias in the prenatal patient with direct transfusion, we decided to continue this method and alternate cases, in order to compare the relative response with both the newer and the older methods of treatment.

The patients used in this study were seen in the prenatal clinic at Methodist Episcopal Hospital in Philadelphia. The series consisted of a total of 104 patients, all of whom were duly registered patients with adequate prenatal care. All patients were given a complete physical examination and the routine laboratory studies, including blood count and hematocrit, at the time of initial visit. They were then placed on a standard U.S.P.

hexavitamin preparation and the regular pregnancy diet. All were routinely placed on daily oral iron in the form of a molybdenum oxide-ferrous sulfate tablet. This contained 195 mg. of ferrous sulfate per tablet and patients were instructed to take one tablet three times daily. At thirty weeks' gestation a repeat hemoglobin, hematocrit, and red cell count were performed. Those patients who displayed less than 10.0 Gm. of hemoglobin per 100 ml. blood were then selected for therapy. These patients were treated either with direct blood transfusion or intravenous iron. No attempt was made to separate patients, the method of treatment being on a strict alternating basis. As such, 50 patients received one or more 500 c.c. units of blood and 54 patients received intravenous saccharated iron in divided doses.

#### Technique

The dosage of iron required was calculated in the manner of Briscoe,<sup>1</sup> taking a total of 2,500 mg. of circulating iron as the absolute minimum that may be accepted. (Thus a patient with only 60 per cent hemoglobin required 40 per cent of 2,500 mg. for correction to 100 per cent, or 1,000 mg.) Injections were given three times weekly, with 100 mg. being administered at the first visit and 200 mg. in each injection thereafter provided that no significant side effects were observed. Administration was accomplished with a 20 c.c. syringe and a 20 gauge needle. After a few trials, there was found to be less pain at the site of injection if a venipuncture was first performed with a 2 c.c. syringe and the 20 c.c. syringe loaded with the iron solution then substituted, leaving the needle in situ in the vein. Injections were carried out slowly over a period of approximately 5 minutes.

Calculation of the amounts of blood given to those patients receiving transfusion therapy was not as accurate. The chief difficulty was the procuring of donors to replace the blood given. Then too, blood is uniformly processed in units of 500 c.c. and fractions of this amount are wasteful. Therefore, those patients with less than the required 10.0



Gm. of hemoglobin were merely administered a single 500 c.c. unit of blood. If an unsatisfactory response was obtained, a second and, in a few cases, even a third unit was given.

It must be emphasized that the therapy in each group is not exact with regard to total amounts of iron administered per patient. In those patients treated with intravenous iron a definite effort was made to restore the total amount of circulating elemental iron to 2,500 mg. by administration of appropriate amounts of iron on a milligram for milligram basis. The average amount of iron given per patient in this group was 900 mg. In those patients treated with whole blood, however, the actual amount of iron given per patient was substantially less. Whole blood averages approximately 300 mg. of elemental iron per 500 c.c., and this then is the corrected amount of iron administered to the average patient treated by transfusion. While the comparison is admittedly not strictly scientific, we believe it is justified since it is essentially a comparison between two commonly used clinical procedures.

Following administration of the chosen treatment, all patients were subjected to a repeat blood count approximately 2 weeks after completion of treatment. A final count was done on the fourth postpartum day. Records were kept on every patient in regard to method of therapy, dose, side effects, and total rise in the hemoglobin level.

### Results

The diagnosis of hypochromic anemia was made in all patients. All patients should therefore, have responded to either iron or blood replacement. Fig. 2 shows the comparative response at various pretreatment levels to each method of management. It can be seen that those patients with less than 8.0 Gm. of hemoglobin responded almost twice as well to intravenous iron as they did to blood. This has been noted previously by other investigators.<sup>9</sup> The more severe the anemia, the greater the response to treatment. We believe the greater rise with iron is most likely due to the fact that greater

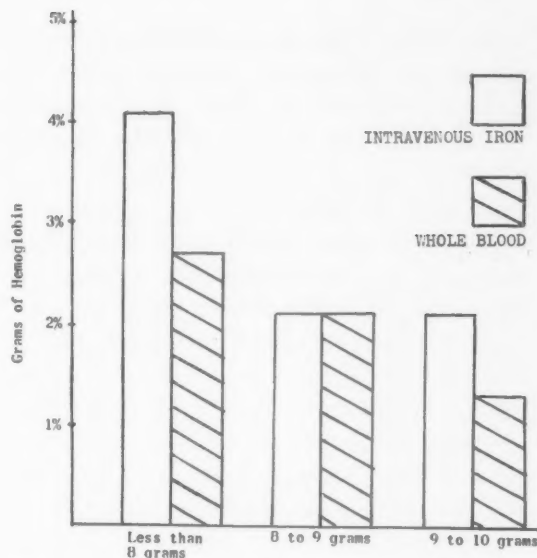


Fig. 2. Response to therapy at various pretreatment hemoglobin levels.

amounts of iron were supplied than were given in those patients receiving blood for therapy. When the anemia was moderate, (between 8.0 and 9.0 Gm. of hemoglobin), the response to both forms of treatment was the same, with a mean hemoglobin rise of 2.1 Gm., the range being from 0 to 3.1 Gm. in the iron group and from 0.7 to 4.0 Gm. in the transfusion group. In those patients with an original hemoglobin between 9.0 and 10.0 Gm., the rise was also similar, averaging 2.1 Gm. for the iron group and 1.3 Gm. for the transfusion patients. The range in response with these patients was between 0.7 and 5.4 Gm. for iron-treated persons and between 0 and 3.2 Gm. for those treated with blood. Two patients in the latter group failed to show any response, despite administration of 1,000 c.c. of whole blood to each. Both patients went into spontaneous labor and were delivered without incident before further treatment. Both displayed postpartum hemoglobin values of 9.9 Gm. per cent. Only one patient in the iron group failed to show any response, and this patient also went into labor before further treatment. The postpartum hemoglobin here remained at 8.4 Gm. and complete hematologic evaluation of this patient failed to reveal any diagnosis other than hypochromic anemia; a long-term follow-up is planned on this patient.

Side effects were encountered in this study as they have been by almost all others who have investigated methods of intravenous treatment. In the patients treated with whole blood, 3 (6.0 per cent) experienced such symptoms; 2 displayed a generalized urticaria readily controlled by administration of Adrenalin and antihistamines; the third developed a precordial pain and syncope which responded to supportive measures without incident. The side effects seen in the group treated with intravenous iron were more frequent in number, occurring on 16 different occasions. These consisted of pain at the site of injection or along the course of the vein (4), nausea (1), flushing (1), syncope (5), dyspnea (2), numbness of the forearms (1), generalized urticaria (1), and acute back pain (1). When one considers that the total number of iron injections given was 279, the percentage of side effects is 5.7, almost the same as in the transfusion group. It should be pointed out, however, that in 3 patients the symptoms were of alarming enough severity to warrant discontinuation of further treatment. In these 3, the presenting symptom was that of dyspnea with or without syncope. Treatment of all side effects, when necessary, consisted solely of supportive measures such as inhalation of aromatic spirits of ammonia, occasional parenteral administration of antihistamines, and, in 2 cases, small doses of Adrenalin. All were fleeting, and the mild ones usually disappeared spontaneously within 2 or 3 minutes.

Eleven patients treated with blood required 2 units for correction of the anemia. Two others required 1,500 c.c. of blood each for correction to a level of 10.0 Gm. of hemoglobin per 100 ml.

#### Comment

The most widely encountered anemia in the prenatal patient is a hypochromic one. It is true that other forms may exist, either as a result of the pregnancy or merely as a complicating and associated problem. In this series, none of the latter were encountered, so it would be expected that all should respond to iron replacement. Since all patients

were treated in early pregnancy with oral iron preparations as a routine medication, those selected for treatment in the later stages of gestation may be considered to have either a poor absorption due to a mucosal block, failure to take the medication, or some other mechanism leading to a failure of assimilation. The problem then resolves itself into one of parenteral administration.

From an economic standpoint, intravenous iron injections are less expensive for the patient than is direct transfusion. The cost of the total amount of iron solution required for a given patient is less than the expense necessary for laboratory processing of whole blood.

Hematologic response to either whole blood or intravenous saccharated iron is adequate for control of these anemias. The problems associated with procurement of donors, laboratory preparation, and actual administration of blood are sufficient to cause us to avoid it if possible. Although occasional side effects are encountered in iron therapy, the good hematologic response, together with ease of administration on an outpatient basis tend to make this a more satisfactory method of management. We believe it to be the method of choice in the average prenatal patient with iron-deficiency anemia.

#### Summary

1. A study is presented comparing two commonly used methods of treatment of hypochromic anemia in the pregnant woman.

2. A general discussion of the metabolism of iron is outlined.

3. A brief résumé of the present methods of iron replacement in iron-deficiency anemia is presented.

4. Alternating cases, 50 patients were treated with transfusions of whole blood, and 54 patients with a total of 279 injections treated by administration of intravenous saccharated iron oxide. Hematologic response was comparable but varied with the initial severity of the anemia, being more pronounced in those patients with a more severe iron depletion.

5. It is noted that the comparison be-

tween these two methods of therapy is not a strictly fair one since the actual amount of iron given per patient is less when the patient is treated by transfusion than that given by intravenous elemental iron replacement.

6. The occurrence of possible side effects and their management are presented.

7. In view of the possibility of transfusion reaction and the difficulties surrounding the procurement and administration of whole

blood, the method of choice of iron replacement in patients refractory to oral therapy was felt to be intravenous iron in divided doses.

We are grateful to Drs. Roy W. Mohler and George A. Hahn for their interest, stimulation, and advice in this study.

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# Gaucher's disease in pregnancy

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GAUCHER'S disease is a rare, hereditary error of metabolism characterized by abnormal storage of cerebroside in reticulo-endothelial cells throughout the body. It was first described by Gaucher in 1882.<sup>5</sup> In 1948, Groen<sup>7</sup> reviewed the literature and reported the results of the thorough study of 6 families in which 21 of his 25 cases occurred. He postulated that Gaucher's disease is due to a mutation, probably in an enzyme system, and is transmitted as a simple dominant trait to approximately 50 per cent of the offspring of affected individuals. The disease tends to manifest itself at a progressively earlier age and, at the same time, it tends to run a more acute course with successive generations. Thus, according to Groen, after having passed through several generations, the disease tends to eliminate itself by causing death in early life or, occasionally, stillbirth.

Groen<sup>7</sup> and Cecil<sup>2</sup> believed that there is no sex predilection, while Harrison<sup>8</sup> stated that the disease occurs more frequently in women. There is general agreement that a large percentage of cases occur in individuals of Jewish descent. The disease may occur at any age, the reported extremes being in a 7-day-old infant<sup>9</sup> and in a 79-year-old man.<sup>15</sup>

Clinical manifestations include splenomegaly, hepatomegaly, enlargement of lymph nodes, especially in the visceral groups, pain and tenderness over the long bones, especially the femurs, pathologic fractures, pallor, hemorrhagic diathesis, pingueculae,

malar flush, myopia, and abnormal pigmentation of skin of legs and face.

Laboratory findings are usually limited to anemia (usually hemolytic), leukopenia, and thrombocytopenia. These findings are manifestations of hypersplenism which develops in a large percentage of patients suffering from Gaucher's disease. Occasionally, a normochromic normocytic anemia is due to myelophthisis from replacement of normal bone marrow elements by the Gaucher cells. Evidence of mild impairment of hepatocellular function is occasionally found in patients with marked hepatomegaly.

X-ray examination may reveal areas of rarefaction in the long bones, especially the femurs. The typical radiologic finding is the "Erlenmeyer flask" deformity in the distal femurs. Occasionally, erosion and compression of the neck of the femur and compression of the vertebrae are found.

Cases occurring in childhood progress rapidly, may be associated with severe central nervous system symptoms, and are usually fatal. In adults, the disease tends to run a chronic course and it frequently is only an incidental finding. In adults, death usually occurs as a result of intercurrent diseases, usually unrelated to Gaucher's disease, rather than as a direct result of it.

Diagnosis is made by the finding and identification of the characteristic cells in bone marrow aspirates or in splenic tissue removed by biopsy or for relief of hypersplenism. Differential diagnosis is essentially that of other causes of chronic splenomegaly.

No specific treatment is known. X-ray irradiation of skeletal lesions is done but the results are not satisfactory. Hyper-

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splenism with the accompanying cytopenias is effectively treated by splenectomy with prompt reversal of the blood picture to normal in most cases.<sup>11, 14</sup> Otherwise, splenectomy does not materially influence the course of the disease.

### Case report

A 20-year-old nulliparous white woman was first seen at Lowry Air Force Base Hospital on Aug. 1, 1956, because of occasional nausea, enlarging and tender breasts, and amenorrhea since May 4, 1956. In June, 1956, the patient, believing herself pregnant, was palpating her abdomen and noted a firm lump on the left side. She did not worry about this lump until she was told that her younger brother was found to have Gaucher's disease with an enlarged spleen.

History revealed that she was easily fatigued during most of her life. She had a tendency to easy bruising and had had recurrent nosebleeds since childhood, never severe enough to require medical attention. Her gums bled slightly but frequently following brushing. On one occasion, following extraction of a tooth, she experienced bleeding from the wound for 12 hours but the bleeding subsided spontaneously. Small accidental cuts never bled excessively. Menstrual periods were very irregular, being absent for as long as 5 to 6 months at times, but the patient denied any excessive or prolonged flow. Shortly before, the patient was told by a physician that she had "mild anemia."

Family history revealed that the patient was of French, Scotch, and English extraction and was a Catholic. There was no known person of the Jewish faith in the entire family. Her parents were well but had not been medically examined in the recent past. A brother, age 12 years, had his spleen removed in July, 1956, because of retardation of growth and cytopenias associated with Gaucher's disease. Another brother, age 21 years, was found to have an enlarged spleen during a routine physical examination and is now known to have Gaucher's disease. Two sisters, ages 11 and 18 years, were examined but no evidence of disease was found. One sister, a "blue baby," died at age 2 days. A paternal uncle died in his twenties of tuberculosis and was said to have an enlarged spleen.

Physical examination revealed the following positive findings: multiple ecchymoses were scattered over the more vulnerable portions

of the body; yellowish elevations resembling pingueculae were seen on the nasal aspects of both bulbar conjunctivae; the mucosal surfaces were pale; a Grade I systolic precordial murmur was noted; there was a moderate tachycardia (102/min.); the spleen extended 19 cm. below the left costal margin in the midclavicular line and also extended 6 cm. past the midline into the right side of the abdomen. The liver extended 8 cm. below the right costal margin in the midclavicular line. Both organs were firm, nontender, and nonnodular. There was no lymphadenopathy. The pregnant uterus was palpable 3 cm. above the symphysis pubis.

Initial laboratory studies were as follows: hemoglobin 10.0 Gm. per cent; hematocrit 27 per cent; red blood cells 2.3 million; white blood cells 4,350; differential 66 neutrophils, 34 lymphocytes; platelets 84,000; bleeding time 2 minutes, 55 seconds; and clotting time 4 minutes, 43 seconds by the Lee-White method. The reticulocyte count was 2.8 per cent; cephalin flocculation 4 plus; alkaline phosphatase 3.25 Bodansky units; bromsulphalein retention 2.5 per cent after 45 minutes; prothrombin time 85 per cent of normal; Coombs test negative; and red cell fragility normal. X-ray film of the chest showed only minimal osteoporosis; films of the lower femurs showed early Erlenmeyer flasklike deformities bilaterally. Bone marrow, aspirated by sternal puncture, was diagnostic of Gaucher's disease.

She was admitted to Lowry Air Force Base Hospital on Aug. 30, 1956. Repeated laboratory determinations revealed that the extent of the cytopenias was greater than previously suspected. Hemoglobin ranged from 5.9 to 7.0 Gm. per cent, hematocrit from 19 to 21 per cent, platelets from 45,000 to 54,000, white blood cells from 1,800 to 2,400, reticulocytes from 4.6 to 5.0 per cent. Red blood cells were 1.5 million. In the hospital, the patient received a total of 3,000 ml. of whole blood over a period of several days. This resulted in a rise of hemoglobin to 12.9 Gm. per cent and hematocrit to 39 per cent.

Dr. Austin Bloch, consultant in hematology from the University of Colorado School of Medicine, felt that the picture was essentially that of hypersplenism and recommended splenectomy. However, he also felt that the poor reticulocyte response in the presence of anemia might be due to the replacement of bone marrow elements by Gaucher's cells. A consultant

in obstetrics felt that the size of the spleen was incompatible with advanced pregnancy.

The patient was readmitted on Oct. 1, 1956, for splenectomy. At that time, the hemoglobin was 8.4; hematocrit 28; leukocytes 2,700; prothrombin time 52 per cent of normal. Before and during the operation she received an additional 3,500 ml. of whole blood. The operation and subsequent recovery were uneventful. No accessory splenic tissue was found in the abdomen. At the time of operation the uterus was noted to be of a size consistent with 4 months' pregnancy. The spleen weighed 2,715 grams and on microscopic examination the sinusoids were seen to be replaced by Gaucher's cells. A wedge biopsy of the liver taken at the time of the operation showed accumulations of Gaucher's cells in the portal spaces and near the capsule (Figs. 1 and 2).

On the fifth postoperative day the hematologic picture was as follows: hemoglobin 15.2; hematocrit 47; white blood cells 11,650; red blood cells 4.67 million; platelets 204,000; prothrombin time 77 per cent of normal; reticulocytes 0.5 per cent.

The tendency to bruise disappeared following splenectomy. She had only two mild episodes of epistaxis and her gums no longer bled. The antenatal course of this, her first pregnancy, was further uncomplicated. On Feb. 15, 1957, she was admitted to Fitzsimons Army Hospital in labor which progressed normally and terminated under pudendal block anesthesia in the delivery of a normal female infant weighing 7 pounds, 7½ ounces. Estimated blood loss at delivery was 250 ml. The postpartum course was entirely uneventful.

She was next seen in the Prenatal Clinic of Fitzsimons Army Hospital on March 21, 1958, with symptoms suggestive of pregnancy. The last menstrual period was on Feb. 8, 1958. Physical examination revealed the presence of pingueculae on the nasal aspect of the conjunctivae bilaterally; there was patchy, brownish pigmentation over the forehead and, to a lesser degree, over the malar prominences. The liver was palpable 8 cm. below the right costal margin. There was a well-healed surgical scar in the left upper quadrant of the abdomen. On pelvic examination the findings were compatible

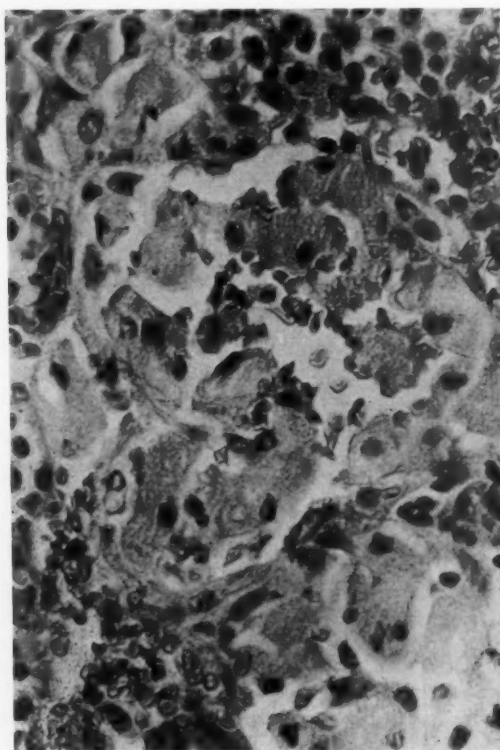


Fig. 1. Spleen. Large lipid-laden Gaucher's cells. ( $\times 900$ ; reduced  $\frac{3}{4}$ .)

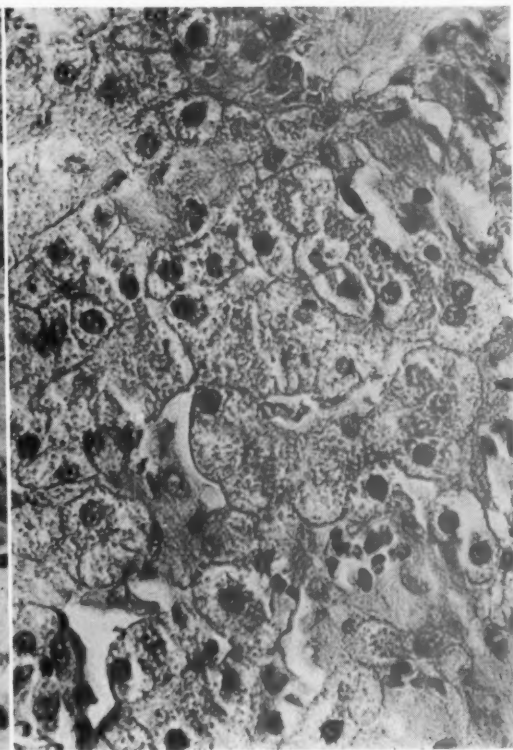


Fig. 2. Liver. Large lipid-laden Gaucher's cells. ( $\times 900$ ; reduced  $\frac{3}{4}$ .)

with the presence of early pregnancy. The hemoglobin was 11.1 Gm. per cent, hematocrit 35, white cells 14,800, and platelets 168,000. Bleeding time was 1 minute, 30 seconds and clotting time 5 minutes, 15 seconds by the capillary tube method. There was no evidence of infection to explain the leukocytosis. She was given oral iron medication and on May 16 the hemoglobin was 11.5 Gm. per cent, hematocrit 35, white cells 13,100.

The prenatal course was uncomplicated until Dec. 10, 1958, when she was hospitalized because of moderate elevation of blood pressure and excessive weight gain which failed to respond to restriction of salt intake, sedation, and diuretics. She was hospitalized for 4 days and was discharged improved. At the time of admission it was felt that induction of labor was inadvisable because of a fairly hard and uneffaced cervix and breech presentation. She was readmitted in labor on Jan. 2, 1959. Labor progressed satisfactorily and the membranes ruptured spontaneously at nearly complete dilatation of the cervix. Shortly after the patient was taken to the delivery room with a footling breech at station plus one with the cervix 9 cm. dilated, it was noted that the cord was prolapsed. Fetal heart tones, noted to be of good quality just a few minutes before, could not be heard. Breech extraction was performed immediately and the 8 pound infant was found to be in good condition. During this procedure the patient sustained a 2 cm. laceration of the cervix. Blood loss during the necessarily rapid procedure was excessive as evidenced by a drop in hemoglobin to 9.7 Gm. per cent. Post partum there was no excessive bleeding. The patient received a transfusion of 1,000 ml. of whole blood which resulted in an elevation of the hemoglobin to 11.2 Gm. per cent on discharge on the fourth postpartum day. Six weeks post partum the patient felt well. Duration and amount of lochia were normal. On physical examination the only essential change was that the liver was palpable only 3 to 4 cm. below the right costal margin. Laboratory studies at that time were as follows: hemoglobin 13.4; hematocrit 41; red blood cells 4.53 million, white blood cells 11,800; differential 59 neutrophils, 39 lymphocytes, 2 monocytes; platelets 473,000; bromsulphalein retention 2 per cent after 45 minutes; cephalin flocculation negative after 48 hours; alkaline phosphatase 9.4 Sincow-Jones-Rinehart units. Radiologic studies of



Fig. 3. Roentgenograms of lower femurs showing increased flaring of distal femurs with thinning of cortex, the early Erlenmeyer flask deformity.

the lower ends of both femurs again revealed changes compatible with early infiltration by Gaucher's cells, but no progression was noted since August, 1956 (Fig. 3). Both children of this patient were examined by a pediatrician, and no evidence of Gaucher's disease was found.

#### Comment

In the English literature there are reported 17 patients who had 40 pregnancies complicated by Gaucher's disease.<sup>1, 3, 4, 6, 7, 10, 12, 16, 17</sup> The above-presented case brings the total to 18 patients with 42 pregnancies. Additional references may be found in the European literature; however, these are not available for review. Pertinent data on these 18 patients with 42 pregnancies are given in Table I. The 42 pregnancies resulted in 32 living children, 10 abortions, one stillbirth, and one maternal death. Four of the abortions were spontaneous, and 6 were therapeutic. The indications for therapeutic

Table I

Author	Gravida	Para	Stillbirths	Therapeutic abortions	Spon-taneous abortions	Anemia	Leukopenia	Thrombopenia	Bleeding tendency	Splenectomy	Size of spleen	Remarks
Bromberg, Toaff, and Diengott	3	2	0	1	0	-	+	-	+	-	2 fingerbreadths above iliac crest	Bleeding tendency anteceded first pregnancy and continued following therapeutic interruption of third pregnancy
Bromberg, Toaff, and Diengott	2	1	0	1	0	+	-	+	+	-	3 fingerbreadths below costal margin	Menorrhagia
Bromberg, Toaff, and Diengott	1	1	1	0	0	-	-	+	+	-	To iliac crest	One of a set of twins died intrapartum of cerebral hemorrhage
Bromberg, Toaff, and Diengott	1	1	0	0	0	+	+	+	+	-	To symphysis pubis	
Bromberg, Toaff, and Diengott	1	1	0	0	0	-	+	U	-	-	2 fingerbreadths above iliac crest	
Bromberg, Toaff, and Diengott	5	2	0	2	0	+	+	+	+	-	To iliac crest	Patient 7 months pregnant at time of report
Bromberg, Toaff, and Diengott	1	1	0	0	0	-	+	-	-	-	4 fingerbreadths below costal margin	
Bromberg, Toaff, and Diengott	4	3	0	1	0	+	+	+	+	+	To umbilicus	Splenectomy in fourth month of third pregnancy
Decker and McWhorter	2	1	0	0	1	+	+	+	+	+	To iliac crest	First pregnancy uneventful; rapid hemodestruction after cessation of cortisone therapy necessitated splenectomy; abortion coincident with an episode of febrile jaundice 2 months after splenectomy
Elliott	1	1	0	0	0	+	-	-	+	+	To iliac crest	Accelerated hemolysis during latter part of pregnancy; splenectomy following uneventful delivery
Gordon and Kaufman	1	1	0	0	0	-	-	-	+	+	To iliac crest	Improvement temporary only
Groen	5	5	0	0	0	U	+	U	U	-	"Large"	Died of postpartum hemorrhage, cause not clear; last infant died on fifth day of life; cause unknown
Groen	2	2	0	0	0	U	U	U	+	+	Unknown	Both pregnancies following splenectomy
Hunter and Evans	3	0	0	0	3	+	U	U	+	+	To umbilicus	Splenectomy at age 47; abortions at earlier age
Logan	4	3	0	1	0	-	-	-	+	+	5 cm. below costal margin; later larger	Therapeutic abortion fourth pregnancy
Pool and Stillman	1	1	0	0	0	U	U	U	+	+	"Large"	Pregnancy after splenectomy
Teton and Treadwell	4	4	0	0	0	-	-	-	+	-	To iliac crest	
Present case	2	2	0	0	0	+	+	+	+	+	19 cm. below costal margin	Acceleration of hemolysis early during first pregnancy; splenectomy during fourth month of first pregnancy



abortion were Gaucher's disease, with or without hemorrhagic manifestations, and anemia. Of the 32 living children, one died on the fifth day of life of unknown causes. The stillbirth occurred in one of the twins reported by Bromberg and associates<sup>1</sup>; it was caused by cerebral hemorrhage. These data do not support the contention of Groen<sup>7</sup> that female patients with Gaucher's disease are frequently infertile, especially in view of the fact that many patients with Gaucher's disease are discouraged from childbearing because of fear of complications. In this respect, the patient reported by Decker<sup>3</sup> is most interesting. Following therapeutic interruption of her second pregnancy, she presented herself 6 months later with a 4 months' gestation, underwent splenectomy at that time, and carried the baby to term and uneventful delivery.

Groen<sup>7</sup> also reports the increased incidence of abortions in patients with Gaucher's disease. Therapeutic abortions should be disregarded in any calculations of abortion rate. If the therapeutic abortions are disregarded, we find that 4 of 37 pregnancies complicated by Gaucher's disease terminated in spontaneous abortions. One of these, reported by Decker and McWhorter,<sup>3</sup> occurred during an episode of febrile jaundice approximately 2 months following splenectomy. The remaining 3 occurred in a patient reported by Hunter and Evans<sup>10</sup>; all 3 were at 8 weeks. This latter patient was reported to have had rather severe bleeding manifestations beginning at an early age. The corrected abortion rate is 11 per cent.

In the management of a pregnant patient with Gaucher's disease, the obstetrician is confronted with several problems. The effect of pregnancy on the maternal disease must be considered. There are no proved deleterious effects of pregnancy on Gaucher's disease. In one case there was an acceleration of hypersplenic activity coincident with pregnancy.<sup>3</sup> However, this is also reported as having occurred independent of pregnancy.<sup>3</sup> Accelerated hemolysis is known to occur in Gaucher's disease with-

out pregnancy. McElin and Mussey,<sup>13</sup> after a thorough review of the subject, felt that pregnancy is a serious complication of the so-called splenic anemia. No instance of Gaucher's disease is found among their cases. Almost exclusively their patients had Banti's syndrome, congenital hemolytic anemia, and idiopathic thrombocytopenic purpura.

The effects of the disease and of its complications on pregnancy are next to be considered. The complications with which an obstetrician is concerned are the cytopenias and the large abdominal mass. Anemia may be severe and may respond poorly or not at all to the usual hematinics. Severe thrombopenia may occur. Leukopenia does not appear to be of primary importance. In spite of the existence of considerable thrombopenia in 6 of the reported patients at the time of delivery and therapeutic abortion, no excessive bleeding is reported. The hemorrhagic tendency manifested itself mainly in the form of bleeding from the gums, ease of bruising, epistaxis, and, in two instances only, moderate menometrorrhagia. Probably the greatest concern of the obstetrician in a pregnant patient with hemorrhagic tendency is uncontrollable postpartum hemorrhage. This is known to have occurred only once, and this resulted in maternal death.<sup>7</sup> The circumstances of this occurrence are not well documented. The patient had four pregnancies without any abnormal bleeding being reported. Uterine inertia, retained secundines, and lacerations of the birth canal cannot be excluded as causes of the hemorrhage. It must be emphasized that most of the reported patients had varying degrees of hypersplenism and manifestations of bleeding tendency.

The problem of an abdominal mass does not appear to be serious. In one of the 18 patients the size of the spleen was not reported; it was enlarged in the remaining 17 patients. Nine patients carried 13 pregnancies to term with spleens enlarged to the vicinity of the iliac crest. No spontaneous abortions occurred in this group. In many of these patients the liver was also enlarged.

The mode of transmission of Gaucher's disease is not known with certainty. Probably the most authoritative work on the subject is that of Groen,<sup>7</sup> who believes that the disease is transmitted as a simple dominant trait. Groen admits, however, that expressivity of the trait is of considerable importance. So called "carrier" patients, without evidence of the disease themselves, may transmit the trait which is later manifested by the disease in part of their offspring. No incidence of Gaucher's disease among the children in this series is reported. It is probable, however, that a considerable number of these children will develop Gaucher's disease later in life. Of interest is the fact that two of the patients in this series had twin sisters.<sup>3, 4</sup> One of these was an identical twin.<sup>3</sup> Both twins had definite anemia and splenomegaly and one had pingueculae, although a definite diagnosis of Gaucher's disease was not established.

The management of the pregnant patient with Gaucher's disease appears to be best directed along conservative lines. There is no justification whatsoever to perform a therapeutic abortion because of the presence of Gaucher's disease or its complications. The only exception may be the rare patient who, following splenectomy, develops recurrent severe cytopenias and bleeding tendency because of excessive replacement of bone marrow by Gaucher's cells. This is not likely to occur during the child-bearing age. Of considerable importance is the fact that many patients carried pregnancies to term before the diagnosis of Gaucher's disease was made. Delivery was uncomplicated in all of these. Symptoms, as a rule, were present at that time.

The value of splenectomy in the correction of cytopenias and bleeding tendency associated with Gaucher's disease is well documented.<sup>11, 14</sup> Splenectomy should be reserved for the severely anemic patient with marked thrombopenia and bleeding tendency. If necessary, splenectomy may be performed during pregnancy. After removal of the spleen, a thorough search for accessory splenic tissue should be performed. One

other case of splenectomy in Gaucher's disease during pregnancy is reported.<sup>3</sup> It was also performed during the fourth month of pregnancy. In both, splenectomy resulted in alleviation of manifestations of marked hypersplenism and did not have any deleterious effects on the coexistent pregnancy. The second trimester appears to be the optimal time for performance of splenectomy during pregnancy if the procedure cannot be postponed until after delivery. It appears to carry the least danger of abortion or premature labor. Less severely affected patients may be carried through pregnancy with judicious use of hematinics and blood transfusions. The anemia of Gaucher's disease may be accentuated by the secondary anemia of pregnancy. The size of the spleen alone is not an indication for splenectomy during pregnancy. Splenectomy may be performed at other times to alleviate symptoms of a large abdominal mass. The use of cortisone to induce remission of hypersplenic activity in Gaucher's disease is reported in one case with return of the hematologic picture to near normal levels.<sup>3</sup> However, after discontinuation of cortisone, the symptoms rapidly reappeared and splenectomy had to be performed. This type of therapy may be of temporary value in selected cases of Gaucher's disease with coexistent pregnancy. X-ray irradiation has no place in the treatment of the pregnant patient with Gaucher's disease. Gordon and Kaufman<sup>6</sup> report that they successfully controlled bleeding in a patient with Gaucher's disease by the intravenous administration of protamine sulfate.

### Summary and conclusions

1. The pertinent literature concerning pregnancy in Gaucher's disease has been reviewed, and a case of two successful pregnancies in a patient with Gaucher's disease is reported.

2. Pregnant patients with Gaucher's disease should be treated conservatively unless marked symptoms of hypersplenism occur.

3. Therapeutic abortion is not indicated by Gaucher's disease or its complications.

4. Pregnancy does not adversely affect Gaucher's disease and the disease does not adversely affect pregnancy.

5. Splenectomy is effective in the treat-

ment of certain complications of Gaucher's disease and may be performed during pregnancy if necessary.

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# Spina bifida occulta and pregnancy

## A case report

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SPINA bifida occulta is an exceedingly common congenital anomaly, being present in approximately 25 per cent of all children. It is defined as "a fusion defect of the vertebral column without protrusion of the intraspinal contents."<sup>3</sup> It occurs most frequently in the lumbar and sacral areas, and most cases are asymptomatic and diagnosis is made incidentally by x-ray examination. There is, however, a small percentage of these patients who have, in addition, some involvement of the central neural axis or the nerve roots. This becomes apparent in several ways—because of either musculoskeletal or sensory disorders of the lower limbs or disturbances in bladder and bowel function. Spina bifida occulta can be localized in several ways; sometimes a cutaneous defect will be found (abnormal hair, small angiomas, lipomas, or a skin dimple) which overlies the bony and nervous defect. Occasionally, there will be present a small intraspinal myelocele which can be demonstrated by myelograms. Of course, the extent of the neurological impairment will vary in different cases depending on the level and extent of the nerve root involvement.<sup>3</sup> Such neurologically affected patients rarely survive into adult life because of intercurrent infections and other fatal complications which occur in childhood. This explains why so few of these cases have been reported in pregnant women. Only 8 such cases have been reported.<sup>1, 2, 4</sup> I wish to report another

case of spina bifida occulta in pregnancy associated with aplasia of the lower sacrum and coccyx and a probable myelocele.

### Case report

M. V. (No. A-43741), a 21-year-old gravida ii, para ii, first came to the office June 21, 1958, with a chief complaint of amenorrhea, her last menstrual period having been April 10, 1958. She stated that she had been born with a spinal defect and that there had been constant dribbling of urine which required a perineal pad. However, she was able to void "normally"—usually 6 or 7 times a day. Also, her bowels had always been "sluggish" so that she rarely had a normal evacuation and, therefore, required frequent enemas. She stated that her sexual life was normal and that two previous pregnancies were "without complication."

Pelvic examination disclosed the skin of the vulva to be excoriated and thickened. There was a marked uriferous odor, and urine dribbled from the meatus during the examination even though the patient had just voided. The uterus was soft and enlarged and the rectum was greatly dilated with a large amount of hard fecal material. The anus lacked sphincter tone; there was no descensus uteri, cystocele, or rectocele; the bony pelvis was gynecoid.

All during her prenatal course, she had 15 to 20 white blood cells per high-power field in the urine, and a 1- or 2-plus albumin. On October 13 she experienced severe right and left lower quadrant pain, and a diagnosis of acute cystitis was made. A wide-spectrum sulfonamide (Azo-Gantrisin) produced rapid improvement. However, on November 2 she experienced a relapse and was admitted to the hospital. Catheterization after voiding produced 50 c.c. of cloudy urine with a 2-plus albumin and 30 to 50 white blood

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cells per high-power field. She again improved rapidly on Azo-Gantrisin and was discharged in 3 days. She was admitted to the hospital in labor on Jan. 20, 1959, and after 2 hours was delivered of a 6 pound, 13 ounce boy who was apparently normal. She seemed to experience the usual amount of pain during the first stage of labor; however, during the late second stage no bearing down reflex was noted.

Immediately postpartum, x-ray examination of the lumbosacral region revealed a spina bifida occulta of S-1 with complete absence of S-4, S-5, and coccyx. The nonprotein nitrogen was 32 mg. per cent and the intravenous pyelogram showed only a very mild hydronephrosis on the right. A urological consultant made a diagnosis of autonomic neurogenic bladder secondary to the nerve defects associated with the spina bifida occulta. Orthopedic examination revealed normal gait, reflexes, and muscle development of the legs. The neurosurgeon felt a small subcutaneous mass over the posterior aspect of the upper sacrum and made a diagnosis of spina bifida occulta of S-1 with probable myelocoele and stated no treatment was indicated. Post partum, although voiding, she had a residual urine varying from 10 to 50 c.c., and she was placed on Azo-Gantrisin from the day of delivery until discharge. She had no bowel movements while in the hospital and required several enemas for evacuation. She was checked at 3 weeks post partum in the office and a residual urine of 20 c.c. was found.

#### Comment

No two of these nine cases are exactly alike because of the endless variations

possible with congenital anomalies. However, they do present certain common clinical problems. First, chronic urinary tract infection which impairs kidney function in time is often present before pregnancy. This seems to be aggravated by the physiological changes of gestation. This complication should be anticipated and promptly treated to minimize further kidney damage. Second, severe spina bifida is often associated with bony deformity of the legs and pelvis which makes cephalopelvic disproportion a real danger. Third, if the spinal cord defect is low lumbar or sacral (as in the present case) labor will probably be somewhat less painful than normally—the amount of pain decrease depending on the level and extent of the nerve involvement. Uterine motor activity should be normal, however, because, like the heart, uterine action is under intrinsic control. Normal delivery has been reported in paraplegics and after bilateral lumbar sympathectomy.<sup>5</sup>

#### Summary

1. A case of spina bifida occulta with aplasia of the lower sacrum and coccyx and probable myelocoele is reported.

2. Problems in the obstetrical management of this type of case are discussed which may become more common as more of these patients reach adult life in the modern antibiotic era. Careful management will decrease fetal loss and maternal morbidity.

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# Extrapyramidal effects due to perphenazine (Trilafon)

Report of 3 cases of stiff-jaw sign

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NAUSEA, vomiting, and anxiety are frequently symptoms in obstetric and gynecologic patients. The use of antiemetic and tranquilizing agents, therefore, is an increasing tendency in this specialty. Clinical experience has demonstrated that these drugs have the potentiality of producing unpleasant and rarely serious side effects.<sup>1-3</sup>

The following report is made of 3 consecutive cases of a hitherto unreported neuromuscular complication produced by perphenazine (Trilafon).

**Case 1** (34040). This 21-year-old gravida i, para 0, was first seen in the office by one of us (P. K.) on March 7, 1959, with amenorrhea, nausea, and vomiting. A diagnosis of intrauterine pregnancy, 6 weeks, complicated by hyperemesis gravidarum was made and Trilafon, 4 mg. tablets 3 to 4 times a day, was prescribed. On March 11, 1959, the patient returned to the office because of persistent nausea and vomiting and complained of stiffness of the lower jaw. She was apprehensive and stated that she felt she was experiencing a stroke. Satisfactory physical examination was impossible because of the patient's anxiety about her condition. Positive findings, however, were clonic and tonic bilateral masseter contractions. The possibility of a hysterical reaction or a dislocation of the mandibular joint due to continuous vomiting was considered. Hospitalization was recommended. On

admission, 50 mg. of promazine hydrochloride (Sparine) was administered parenterally and routine antiemetic treatment, consisting of parenteral fluids, electrolytes, and vitamins, was started. The jaw spasm disappeared soon after admission and no recurrence was noted. The patient was continued on oral Sparine as a tranquilizer. The hospital course was otherwise uneventful and she was discharged on March 15, 1959, in good condition. No further attention was focused upon the jaw.

**Case 2** (33942). This 49-year-old gravida vi, para vi, was admitted to the hospital on March 6, 1959, because of a positive Papanicolaou smear. On clinical and laboratory studies she was found to have squamous cell carcinoma of the cervix, Stage I. Radical abdominal hysterectomy with bilateral node dissection was performed on March 11, 1959. The patient's postoperative course was uneventful except for apprehension and persistent backache which could not be related to any organic pathologic condition. On March 8, 1959, she was placed on meprobamate (Equanil), 400 mg. 4 times a day. On March 12, 1959, perphenazine, 8 mg. tablets 4 times a day, was substituted for meprobamate. On March 13, 1959, after receiving the third dose, the patient complained of a tense jaw and tightness of the right foot. There was a mild opisthotonus position. Eye reflexes, tongue movements, and swallowing reflexes were normal. Upper and lower extremities were normal in mobility, but there was slight extension of the right foot. There were evident tonic and clonic contractions of the left masseter

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muscle which resulted in a marked deviation of the mandible to the left. She complained of pain together with stiffness of the jaw and could not open her mouth completely. The spasm was intermittent and alternated from side to side.

The cause of this was obscure but several possibilities were entertained, including (1) postoperative localized tetanus, (2) tetany, and (3) hysteria. Tetanus was considered unlikely as the spasm was unilateral and not persistent, and no dysphagia or risus sardonicus developed. Blood calcium level was 4.7 mEq. per liter and carbon dioxide capacity 28 mEq. per liter. Therefore, hysteria was considered again as the most likely cause of the findings. Sparine, 50 mg. intramuscularly, was administered with partial relief. Additionally, 200 mg. of Sodium Amytal was given intramuscularly. The patient was able to sleep comfortably following this. The next day, localized, residual muscle spasm persisted. Perphenazine was continued with satisfactory relief of anxiety.

**Case 3 (34022).** This 33-year-old multipara was admitted to the hospital with persistent dysfunctional uterine bleeding, lacerated perineum, rectocele, and partial uterine descensus. A vaginal hysterectomy with colpoperineorrhaphy was performed on March 11, 1959. The post-

operative course was uneventful except for urinary retention. On March 13, 1959, perphenazine, 4 mg. tablets 4 times a day, was administered. On March 14, 1959, the patient complained that her jaw was sliding to one side (Fig. 1). She was extremely apprehensive and unable to open her mouth completely. On examination, severe clonic and tonic contractions of the masseter muscles were noted. These were more pronounced on the left, resulting in a deviation of the mandible to that side. There was marked stiffness of the lower jaw. Eye, neck, and tongue movements were normal. Deep tendon reflexes were hypertonic. Babinski, Oppenheim, and ankle clonus signs were negative. Abdominal skin reflexes were normal. Spasm of the muscles innervated by the trigeminal nerve was the predominant finding again, in this third patient. Tetanus and tetany were again considered but rejected as unlikely on the basis of clinical findings. Despite the administration of Sodium Amytal and Sparine, intermittent episodes of clonic and tonic jaw muscle contractions continued. On March 15, 1959, perphenazine was discontinued. Six hours later the patient had no complaints and the previous findings had disappeared without recurrence (Fig. 2).



Fig. 1. Patient in Case 3 during contraction of the masseter muscle due to Trilafon.



Fig. 2. Same patient after Trilafon was discontinued and the contractions disappeared.

**Comment**

The appearance of 3 consecutive patients unknown to each other, with the finding of the stiff, painful jaw, on the same hospital service, prompted us to search for a common etiological agent. Since this type of stiff jaw could not be related to a known clinical entity, the possibility of a previously unknown syndrome was considered. First thought was given to the involvement of the trigeminal nerve by an infectious agent, possibly a virus, but this was not considered seriously because further reflection prompted the realization that all 3 patients had in common received perphenazine. This drug was used to relieve anxiety in each case. This led us to the conclusion that the symptoms were due to extrapyramidal effect of perphenazine, resulting in a previously undescribed stiff-jaw sign. The symptoms disappeared upon discontinuance of the drug in all 3 patients.

In one of the few published papers about this potent drug, side effects were described to be paradoxical anxiety, nausea, and vomiting.<sup>4</sup> A case of sustained convulsive seizures has been recently reported in a patient in the eighth week of pregnancy. A fine tremor of the jaw was observed prior to convulsions.<sup>5</sup> Extrapyramidal and Parkinson-like effects following doses above 15 mg. have been mentioned in the manufacturer's printed material.

Perphenazine has been used lately in large numbers of cases as an adjunct to narcotics in labor and as a hypotensive drug in toxemia of pregnancy. Gready<sup>6</sup> reported 700 obstetric patients in labor in whom perphenazine was used in a dosage of 5 to 25 mg. (mostly 10 mg.) in addition to other analgesics. No side effects or toxicity signs were described. Birnberg<sup>7</sup> reports 67 office patients in whom perphenazine, 8 mg. suppositories was used 2 times daily for nausea and vomiting of pregnancy. None of the patients were reported to have side effects other than mild drowsiness and dizziness. Despite the fact that very few instances of complication with this drug have been reported, our 3 cases were rather striking. Three out of 34 private patients in our practice in whom Trilafon was used as a tranquilizer or antiemetic developed the same type of neuromuscular complication involving mainly masseter muscles innervated by the trigeminal nerve.

**Summary**

Recent reports indicate that perphenazine is being used extensively in obstetric and gynecologic practice. Clinical reports of complications due to this drug are rare. Three patients are reported in whom a new sign, stiff jaw, is described as a side effect of this tranquilizing and antiemetic agent.

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# The maternity services in Britain and the British obstetrician

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MANY transatlantic visitors to Britain, and especially doctors serving in the United States Armed Forces here, ask about the British National Health Service and in particular about the maternity services and the life and work of the British obstetrician. This short account of the present position may therefore be of interest to the readers of this JOURNAL.

## The British National Health Service

The National Health Service (N.H.S.), instituted in 1948, entitles every individual in Britain, whether resident or visitor, to free medical, nursing, and hospital care. The population of England, Wales, and Scotland together is nearly 50,000,000. The annual cost of the N.H.S. is now about \$220,000,000, of which about 10 per cent represents the drug bill. The major part of the cost falls on general exchequer funds. A small contribution comes from part of the National Insurance payments levied on all who work. A relatively minute proportion comes from fixed charges for specific services (e.g., fourteen cents for each prescription filled) and for some special appliances (e.g., \$1.40 for an elastic stocking).

In order to avail himself of the facilities of the N.H.S. the individual must first enroll on the "list" of a local general practitioner, and 99 per cent of the population have so enrolled. A person can, if he wishes, change from one general practitioner to another in the same area, or to one in a different area if he changes place of residence.

*Other than in accident or emergency, an individual has no direct access to a specialist or hospital except through his general practitioner.*

The N.H.S. is divided into three sections:

1. All hospitals and their staffs are controlled by Regional Hospital Boards, of which there are 19. In England and Wales, but not in Scotland, the "teaching hospitals," at which the students of the local university medical school receive their clinical instruction, are separately organized under their Boards of Governors, which, however, collaborate closely with the Regional Boards.

The Boards provide all specialist services, including maternity, throughout the country in the form of hospitals and clinics, and all hospital doctors and midwives are under contract to the area Boards. The latter also maintain a panel of their specialists who are available to be called in by the general practitioner to see the patient at home when this is necessary on medical grounds; this is a "domiciliary consultation," for which the specialist receives an extra case fee. In most areas the hospital maternity units organize emergency obstetric teams ("flying squads") to treat emergencies in the patients' own homes. Usually the patient is made safe for transfer to hospital (e.g., in antepartum hemorrhage), but sometimes treatment is successfully concluded at home (e.g., for retained placenta).

2. The second part of the N.H.S administrative setup is formed by the general

practitioners, of whom there are about 21,000. These family doctors are under contract to their Local Executive Council, of which there is one for each major local authority area, to provide full general medical care for every person on their individual lists. A general practitioner is allowed up to 3,500 persons on his list but the average is 2,250. For each of these he is paid an average annual capitation fee of \$3.00, irrespective of how often or how seldom that person calls on his services. As will be seen later, maternity work is one of the few services for which the family doctor receives a case fee additional to the capitation fee.

In order to obtain an even distribution of family doctors, certain areas are designated as "closed," where no more general practitioners will be allowed to have a list under the N.H.S.; while in a few isolated regions special financial inducements are offered to attract doctors to practice. Generally it is difficult for a family doctor to move from one N.H.S. practice to another. The general practitioner may accept for treatment as a private patient, for a fee, anyone who is not on his list, but there are a few doctors who confine themselves to such private general practice. Ninety-nine per cent of the population are registered with an N.H.S. doctor, with freedom to change from one to another, and anyone who obtains a prescription from a private doctor must pay the full cost of the drugs as against the flat rate of fourteen cents for an N.H.S. prescription. These facts tend to limit private general practice, but there is some pressure on the Ministry of Health to allow all prescriptions, whether N.H.S. or private, to be charged at the same rate.

3. The third constituent part of the N.H.S. is formed by the local Health Authorities, of which there is one for each urban or county area. They are responsible for all public health and domiciliary services not already mentioned. Through their Medical Officers of Health they organize maternity and child welfare clinics, control the area domiciliary midwives, health visitors, and other auxiliaries, and are responsible

for the ambulance services. It is a disadvantage of the local authority antenatal clinics that they are largely staffed by public health doctors who practice no obstetrics other than antenatal care. At one time these clinics filled a gap, but now attendance is falling as both hospitals and general practitioners have more and more undertaken the antenatal supervision of their own patients.

#### Place of delivery

Hospital maternity beds are located either in special maternity hospitals or in separate maternity units in general hospitals. Of all hospital beds, 3.7 per cent are allocated for obstetrics and 2 per cent for gynecology. There are also, but mostly outside urban areas, a few small maternity homes, under the control of the Regional Boards and the general supervision of the Boards' specialists, where the local general practitioners may deliver their own patients; about 6 per cent of all labors in 1956 took place in such general practitioner-staffed units. In the 3 countries altogether, there are about 800,000 deliveries a year. In 1956, 64 per cent of these were institutional as compared with 50 per cent in 1947.

At present there are not sufficient hospital maternity beds to allow all labors to take place institutionally; nor even sufficient to satisfy the growing demand of all the women who want to be delivered in hospital. Further, presumably for reasons of national economy, until this year no further hospital maternity beds were to be provided in any area in which there were already enough to allow 50 per cent of deliveries to take place in the hospital. A scheme of priorities for hospital delivery had therefore to be laid down; preference is given to women with past or present medical or obstetrical complications, primigravidas, women in their fifth or subsequent pregnancy, and those who cannot be delivered at home for social reasons, most often inadequate housing.

This situation is naturally a source of dissatisfaction to doctors and patients alike. The pregnant woman would like to have

her baby in the place of her choice, and in probably over 80 per cent of cases this is a hospital. The specialist obstetrician would like to offer a hospital maternity bed to every woman who wants or will accept one. The family doctor would like the right, at present denied to him unless he is fortunate enough to practice in an area with a general practitioner-staffed maternity home, to deliver his own normal cases in a fully equipped maternity unit. A possible solution to the first 2 of these problems would be to reduce the present 10 day stay in hospital of normal puerperas to 3 days, as is done in other countries. But there are difficulties. Most large hospital maternity units are training schools for midwives, and the Central Midwives Board might withdraw recognition, and pupils, from a hospital introducing this policy. Nor would most domiciliary midwives be content to see their status reduced to that of a maternity nurse, although some obstetricians see this as an inevitable if not immediate change. And it would mean a radical departure from tradition.

Of the women who cannot or do not want to be accepted for delivery in hospital under the N.H.S., most are delivered at home under the care of a domiciliary midwife or family doctor or both. A few, probably less than 4 per cent of all pregnant women, elect to make private arrangements at their own expense for their obstetric care. They are delivered either by a specialist in an N.H.S. hospital which has accommodation for private maternity patients, or in one of the relatively few private maternity nursing homes, or in their own homes; alternatively they may engage their family doctor to deliver them in either of the latter two places. The charges for private accommodation in hospital or nursing home, excluding doctor's fees, etc., are about \$6.00 to \$15.00 a day, the average being \$8.00 to \$10.00. It is remarkable that while there are several private insurance schemes which will cover the subscribing Briton against private hospital and medical fees, there is none which includes normal obstetric care.

The tripartite administrative setup of the N.H.S. militates against smooth running, and the efficiency of the maternity services not unexpectedly varies in different areas according to the degree of cooperation achieved between the 3 component parts; but it takes time for an efficient system to be evolved and the N.H.S. is only 10 years old. That there are defects in the present setup was acknowledged when, in April, 1956, a Committee on Maternity Services (the Cranbrook Committee) was set up to review the present organization.

The Cranbrook Committee published its report in February, 1959. Among its recommendations, any or all of which may or may not be accepted by the Ministry of Health, are the following:

1. No alteration in the present tripartite administrative structure of the maternity services.
2. Sufficient hospital maternity beds for 70 per cent of all confinements and sufficient antenatal beds for 20 to 25 per cent.
3. All general practitioner-obstetricians to have access to general practitioner maternity beds, and the number of the latter to be increased.

#### **The professional structure of the British maternity services**

The administrative structure having been outlined, an account must now be given of the professional structure of the maternity services. This comprises midwives and doctors, the latter group consisting of medical students, interns, general practitioners, and specialists in the various stages from trainees to the top grade of consultant specialist.

**The midwife.** It is important to realize the very large part played by the midwife in British obstetrics. The earlier division of midwives into institutional and domiciliary, with the former employed by the hospitals and the latter by the local authorities, has been continued under the N.H.S. There are now about 7,000 qualified midwives in hospitals, 20 per cent of them working part time. There are about 7,500 in domiciliary



practice, but 60 per cent of these are part time, many acting also as district nurses or health visitors.

The clinical responsibility of the midwife is less today than 15 years ago, partly because there are now more doctors working in the hospital maternity units and partly because the woman having her baby at home can now, without cost, be attended by a doctor as well as a midwife. Nevertheless, over 75 per cent of deliveries in hospital are conducted by midwives, or by pupil-midwives or medical students under the personal supervision of a midwife. The midwife does not take complete responsibility for all these labors for most of the patients are seen at some stage of labor by one or more doctors, with the midwife acting as a member, albeit an important member, of the obstetric team. It may be deduced from the above figure that the proportion of operative deliveries (forceps and sections) is much lower in British than in American hospitals. With respect to *home confinements* although in about 80 per cent of these in 1958 a general practitioner was booked to provide maternity services, in only 20 per cent was he present at delivery. *In order to qualify for his case fee, the family doctor need not attend during labor, unless he thinks it necessary or is summoned by the midwife.*

The Central Midwives Board (C.M.B.) is the statutory body responsible for the training, certification, registration, and practice of midwives. The practice of the midwife, the scope of her work, her use of drugs including analgesics, and the occasions on which she *must* call in a doctor are all rigidly laid down in the rules of the C.M.B.

The training of the pupil-midwife is in two parts. The first period—6 months for a qualified general or children's nurse and 18 months for others—is spent in a recognized hospital maternity unit where the student learns both theory and practice. The pupil must deliver under supervision not less than 10 women and nurse not less than 50 puerperas. The first examination, written and oral, must then be passed before the pupil can go on to the second part of her

training. The latter lasts for 6 months, 3 of which are spent attending patients outside the hospital under the close supervision of a practicing domiciliary midwife. During this 6 months the pupil must deliver not less than 20 women, at least 10 of them in their own homes. The second examination, oral and clinical, must then be passed before the nurse can be enrolled as a State Certified Midwife (S.C.M.). For those who wish to train as a Midwife Teacher there is a further course of wider studies leading to a Diploma examination.

About 3,000 midwives qualify each year, but only about 25 per cent of these are still practicing midwifery 3 years after qualification. This is because many return to other branches of nursing or become health visitors, while others leave nursing altogether for married life or for nonnursing employment. There is no shortage of successful pupil-midwives, but too small a proportion of them continue in midwifery after qualification.

The pupil-midwife is paid \$900 a year, less \$365 deducted by the hospital for board and residence. If she was previously a registered general nurse this means a fall of at least \$300 a year in her take-home pay while she is learning midwifery. The qualified midwife is on a scale of \$1,375 to \$2,000 a year, less \$480 to \$510 if resident, with higher rates for the relatively few more responsible posts. The midwifery tutor with her extra diploma gets \$1,980 to \$2,300 a year, less \$600 if resident. It will be realized that resident staff, and this applies to doctors, too, have a fixed sum deducted for board and residence in the hospital, the amount varying directly with the height of the individual's status.

**The medical student.** The medical course in British universities takes 6 years, including a first or premedical year from which one can be exempted if suitably qualified. The cost of the 6 years, the last 3 of which are occupied mainly in clinical instruction, is about \$1,500; this includes fees, books, and instruments but excludes all living costs.

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they are later practiced, as one integrated branch of medicine. The General Medical Council, which governs the education of medical students and their examinations, does not lay down a precise syllabus but specifies (1) systematic instruction in the principles and practice of midwifery and gynecology; (2) clinical instruction in midwifery and gynecology, and attendance on the practice of a hospital maternity unit and on inpatient and outpatient gynecological practice; (3) not less than 2 months of the time devoted to clinical instruction in midwifery should be spent by the student in residence in a hospital maternity unit, during which period he should personally conduct an adequate number of labors. Instruction should emphasize antenatal and postnatal care, the management of normal labor and its minor complications, the impact of pregnancy on general disease and vice versa, and the care of the newborn. The management of major abnormalities of labor should be taught in principle rather than in detail.

The medical student eventually graduates as a Bachelor of Medicine and Bachelor of Surgery (M.B.,Ch.B. or M.B.,B.S.). He is registered only provisionally until he has completed one year of hospital internship, after which he is fully registered as a medical practitioner. The degree of Doctor of Medicine (M.D.) is in Britain a higher postgraduate degree obtained by thesis or examination.

**The general practitioner.** Every registered medical practitioner is entitled to practice obstetrics but in fact midwifery practice is confined to general practitioners and to hospital obstetric medical staff of all grades from trainees to full specialists.

During a woman's pregnancy the general practitioner on whose list she is included is still responsible for her general medical care, except while she may be in a specialist-staffed hospital. If she wishes to book for delivery in a hospital, or to come under the private care of a specialist, she must be so referred by her family doctor. If she asks her general practitioner to provide ma-

ternity services for her, with confinement to take place in her home or in a national health service or private maternity home, he receives a case fee additional to his annual capitation fee for the patient.

In England and Wales (but not in Scotland) for the purpose of maternity services general practitioners are divided into two classes—those on the obstetric list and those not. The former receive a case fee of \$21 for obstetric care, the latter \$15. Originally no rigid qualifications were laid down for the inclusion of a doctor on the obstetric list and about 75 per cent are now so included. But now in more and more areas 6 months postgraduate resident experience in a hospital maternity unit is being required before inclusion on the list. The Royal College of Obstetricians and Gynecologists (R.C.O.G.) has long maintained that domiciliary midwifery should be restricted to those doctors with extra postgraduate experience, and in 1933 instituted a Diploma in Obstetrics (D.Obst.R.C.O.G.) designed to set the seal of practical postgraduate experience on those intending to act as general practitioner-obstetricians. To sit for the examination the doctor must have held at least a 6 months' resident hospital post in surgery or general medicine as well as a 6 months' resident obstetric post in an approved hospital; but the College emphasizes that the prescribed period of training is more important than the examination. Among their recommendations to the Cranbrook Committee, the R.C.O.G. included elevation of the status of the general practitioner-obstetrician, with minimum requirements in postgraduate training and continuing adequate practical experience.

In its report in 1959, the Cranbrook Committee accepted these recommendations but went further in proposing that the doctor not on the obstetric list should receive no payment at all for maternity work. The general practitioner-obstetrician feels strongly that the case fee should be increased. Certainly, to do justice to his obstetric commitments, he would have less time for general medical practice and could not cope with

anything like a full list of 3,500 persons. Such an increase in case fee, it is strongly felt, should be accompanied by a raising of the minimum requirements now having to be fulfilled to qualify for the fee. At present the doctor is required at least to perform an initial antenatal examination and a further examination at about the thirty-sixth week; attend during labor and the puerperium if he thinks it necessary or if he is summoned by the midwife; and make a postnatal examination about 6 weeks after delivery. Few doctors fail to give much more than these minimum services, which they regard as most inadequate for a good standard of practice.

At all times the family doctor has behind him all the resources of the hospital services. He may call out a specialist, whether in obstetrics or in any other specialty, to visit the patient in her own home for consultation. Incidentally, for this "domiciliary consultation" the specialist is paid \$12, which compares oddly with the \$15 or \$21 which the general practitioner receives for the woman's whole obstetric care. In most areas, too, the doctor can call on the hospital-based obstetric "flying squad" to deal with acute emergencies in the patient's own home; hemorrhage is the commonest such emergency.

**The obstetrician in training.** The most junior grade of hospital post is that of *house officer*, the tenure of which is 6 months. Most house officers in obstetrics later enter general practice, many of them taking the D.Obst.R.C.O.G. as tangible proof of their extra experience and ability.

The doctor who intends to specialize in obstetrics and gynecology proceeds to fulfill the requirements of the Membership examination (M.R.C.O.G.), for this degree is now regarded as the higher qualification required for full consultant specialist status. In some centers, notably in the teaching hospitals, preference is given to those candidates for consultant posts who are also Fellows of one of the Royal Colleges of Surgery (F.R.C.S.). Fellowship of the R.C.O.G. is by election from Membership after recom-

mendation to the College Council.

The aspirant specialist proceeds to obtain posts in obstetrics and gynecology first as *senior house officer* (tenure one year) and then as *registrar* (tenure two years). The rates of pay for these posts are as follows, the figures in parentheses being the amounts deducted for board and residence: House officer: \$1,400 to \$1,560 a year if provisionally registered (i.e., within the year of compulsory internships), and \$1,730 if fully registered (\$360). Senior house officer: \$2,540 a year (\$440). Registrar: \$2,800 first year and \$3,180 second year (\$510).

The next grade is that of *senior registrar*, and the aspirant for this appointment is expected already to have passed the M.R.C.O.G. examination. To sit for the M.R.C.O.G., the doctor must have: (1) been qualified at least 5 years; (2) held resident medical and surgical posts in recognized hospitals, each of at least 6 months' duration; (3) held a 12 months' resident obstetrical post in a recognized hospital unit; (4) held a 12 months' resident gynecological post in a recognized hospital unit (these last two requirements may be combined in one or more posts, but they must cover 2 years in all with at least 6 months in any one post); (5) regularly attended recognized antenatal, postnatal, and child welfare clinics for at least 6 months; (6) submitted and had accepted complete records of 20 selected obstetrical and 20 selected gynecological cases treated by him under the supervision of his consultants, as well as one obstetrical and one gynecological commentary of 2,000 words each on subjects preferably pertaining to some of the cases.

The examination itself consists of two written papers of 3 hours each; a clinical examination; and *viva voce* examinations in obstetrics and gynecology and in pathology. The standard of the examination may be judged from the fact that out of 241 candidates in 1956, 79 (32 per cent) were successful.

The senior registrar normally holds this post for 4 years but his tenure may be extended. His next appointment is normally

to the highest grade, namely, as a *consultant specialist*. The senior registrar is on a pay scale of \$3,600 to \$4,600 a year (\$600).

There are always plenty of applicants for house officer posts in obstetrics. Most are seeking experience before entering general practice, where they aim to give their patients a high standard of obstetric care and where they will be admitted to the obstetric list with its higher case fee. Applicants for registrar posts are usually committing themselves to specialization. But, as will be seen later, there is a fairly rigid establishment of senior registrars and of consultants in Britain, and therefore the chances of reaching the top grade are not so good now as when the service was expanding immediately after the introduction of the N.H.S. in 1948. There are, therefore, fewer candidates now than formerly for registrar posts, especially outside the teaching hospitals. Many such appointments are filled by doctors from the British Commonwealth and other overseas countries, who come to Britain to obtain concentrated experience and to qualify to sit for the M.R.C.O.G. Most return to their own countries to practice as specialists, but the training of these men and women is a most valuable service performed by British obstetrics and obstetricians.

**The specialist obstetrician.** When a doctor has obtained his M.R.C.O.G. he is theoretically a specialist in obstetrics and gynecology, but he is unlikely to obtain a specialist post as a consultant in the N.H.S. before the end of 3 or 4 years as a senior registrar and often it is much later. His tenure of office may be extended until he does obtain a consultant post. Or he may spend a year or more in a university department of obstetrics and gynecology, doing research or teaching or both, as well as assisting in the clinical work of the professional unit. Or he may spend some years acquiring an F.R.C.S. Or he may give up the specialty and turn to another branch of medicine, probably general practice. Or he may emigrate.

It must be emphasized that a specialist is not economically viable unless he has an N.H.S. appointment. This is because (1) there is no direct access of patient to specialist, for she must be referred by her general practitioner; (2) to the local practitioners the specialist who holds an N.H.S. consultant post has the appropriate "hall-mark"; they expect him to provide a good service for their N.H.S. patients and will therefore send anyone wanting private specialist treatment to him rather than to someone outside the N.H.S.; (3) there are very few hospitals outside the N.H.S. in which a private specialist can treat his patients; (4) over 99 per cent of the population are on general practitioners' lists and can have all the specialist and hospital facilities of the N.H.S. free, whereas they have to pay fees to a specialist working outside the N.H.S. as well as charges for private accommodation. The amount of private practice in obstetrics is small—probably less than 4 per cent of all pregnancies.

There is, therefore, no economic future for the senior registrar in Britain *outside* the N.H.S. What are his prospects of advancement *inside* it? Here are some relevant figures for 1957. There were about 25 senior registrars in or beyond their fourth year of office, with about another 15 of their fellows due to enter their fourth year each following year. There were 500 consultants in obstetrics and gynecology, of whom only 44 were over 60 years of age, that is within 5 years of retirement age. And in the previous 5 years there had been little expansion of the total establishment of consultant posts—there were 473 in December, 1952, 493 in December, 1955, and 500 in December, 1957.

**The appointed consultant.** A consultant may be employed either full time or part time by the N.H.S. Most elect for the latter alternative because they feel more independent and because they are then able to pursue private practice too, but others are of a temperament which finds whole-time status more congenial.

The full-time consultant is on a basic



pay scale of \$6,600 to \$9,750 per annum. The part-time consultant is paid X-elevenths of the full-time rate, where X = number of half-days he works each week for the N.H.S. +  $\frac{1}{4}$ . Thus, for 8 half-days or "sessions" per week he receives  $\frac{3}{4}$  of the whole-time rate, his scale then being \$4,950 to \$7,315 per annum.

In addition to his basic pay, the consultant, whether whole-time or part-time, can add to his N.H.S. income by the following:

1. *Domiciliary consultations.* A consultant called by a general practitioner to see a patient in her own home for medical reasons receives a case fee of \$12. If he performs an obstetric operation there he is paid an additional \$12. The part-timer is allowed to earn a maximum of \$2,400 each year in this way but his whole-time colleague is restricted to a ceiling of \$2,010 a year.

2. *Distinction awards.* These are made for "special merit" to a fixed proportion of consultants. There are three grades of awards, 20 per cent receiving \$1,500 a year, 10 per cent getting \$4,500, and 4 per cent, \$7,500. The allocations of these awards are not published and for this and other reasons there is some disquiet about them.

3. *Mileage payments.* A mileage allowance of about ten cents a mile can be claimed on journeys on duty.

The part-time, but not the full-time, consultant can also participate in private practice. The amount earned by the specialist in this respect varies enormously according to his standing and the area in which he works. An average fee for a private consultation is \$15, and for complete obstetric care, \$100 to \$300, with an average nearer \$150. When a private patient is accommodated in an N.H.S. hospital, the specialist's fees must be in accordance with a fixed scale; e.g., a hysterectomy carries a fee of up to \$150. A patient in a private ward *must* engage a private specialist. On the other hand, the consultant cannot charge any fee for any services to a patient in a general ward.

A consultant normally retains his N.H.S.

appointment until the retiring age of 65. He contributes 6 per cent of his N.H.S. pay to superannuation, the N.H.S. adding 8 per cent. He is allowed 6 weeks' annual leave, and may also obtain study leave, with or without expenses at the discretion of his Regional Hospital Board, for medical meetings and conferences.

**University appointments.** All the professorial chairs in Britain are of obstetrics and gynecology combined and all the professors are whole time. In most universities the professor is not allowed any private practice, but in a few he is permitted a small amount with the fees being retained by the university, although they may be earmarked for his department. The professor (\$9,000 a year) and his chief assistant (senior lecturer, \$5,400 to \$7,500 a year) are graded as consultants and are loaned by means of honorary contracts to the teaching hospitals for their clinical work. They are eligible for distinction awards like other consultants. The more junior members of the professorial unit are graded as registrars or senior registrars.

The professor and his full-time staff do not undertake all of the systematic and clinical teaching of the medical students. Their consultant colleagues in the teaching hospitals are paid a small annual fee by the university for acting as part-time instructors (clinical lecturers).

### Conclusion

The National Health Service in Britain is only 10 years old and it is still evolving toward a more smooth-running machine. It has had some influence on the training and practice of the obstetrician and gynecologist, chiefly by virtue of a rather inflexible numerical establishment of specialists and senior trainees. But the standards of teaching and practice remain in the hands of the profession itself, under the leadership of the Royal College of Obstetricians and Gynecologists.

If one may look into the future, it seems likely to bring a higher proportion of deliveries occurring in hospitals, a restriction

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of general practice obstetrics to those family doctors with extra experience and skill, and a diminution in the stature of the midwife with perhaps the creation of a new grade of maternity nurse.

Meanwhile, the following statistics for England, Wales, and Scotland for 1957

may be quoted as a yardstick of the efficiency of the present setup. Total births numbered 840,351. The maternal mortality rate was 0.47 per thousand total births. The stillbirth rate was 22.6 per thousand total births. The neonatal death rate was 16.8 per thousand live births.

# Office vaginal examination in pregnancy

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FEW obstetricians question the value of a pelvic examination performed during the last month of pregnancy. In spite of this, there are two principal deterrents to this practice. The first is the traditional taboo associated with vaginal examination at the end of pregnancy. The second is the annoyance associated with the performance of a so-called "sterile" vaginal examination. The performance of a simpler, but equally informative, unsterile vaginal examination is almost universally condemned. I have felt that the objections to unsterile vaginal examinations are exaggerated, if not entirely unwarranted. Intermittently for several years and routinely for the past 5 years, therefore, all prenatal patients have been examined vaginally, without aseptic precautions, at the time of each office visit during the last month of pregnancy.

### Theoretical hazards

The greatest deterrent to the performance of unsterile vaginal examination during late pregnancy is the fear of introduction of pathogenic organisms into the birth canal. In this series there were no instances of either prenatal or postnatal morbidity which could be directly or indirectly attributed to the vaginal examinations. The incidence and causes of morbidity in this series are presented in Table I.

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*Read at a meeting of the Obstetrical Society of Philadelphia, Oct. 2, 1958.*

The morbidity rate experienced in this series parallels that encountered in the same practice before the introduction of routine vaginal examinations.

The theoretical possibility of disturbing an unrecognized placenta previa must be considered a potential hazard. If the examination is carried out gently and properly, however, the uterine cavity is not entered. This theoretical complication did not occur in this series.

### Technique

1. The office personnel is instructed to routinely prepare all patients for a vaginal examination at the time of each prenatal visit during the last month of pregnancy.
2. With a clean, sterilized but not sterile, glove and without vaginal or perineal preparation, one finger is inserted into the vagina.
3. The examining finger, aided by fixation of the presenting part from above, determines the presenting part by palpation through the thinned lower uterine segment. A Hillis maneuver is performed at the same time.

Table I. Incidence and causes of morbidity following vaginal examination

Total number of deliveries	2,000
Number of patients with morbidity	40
Incidence of morbidity	2.0%
Causes of morbidity	
Urinary infections	12
Genital infections	18
Phlebitis	2
Breast infections	6
Respiratory infections	2
Estimated number of vaginal examinations	6,000

4. The examining finger is swept over the external os in order to determine the amount of dilatation, the amount of effacement, and the position and the consistency of the cervix. If the cervix is uneffaced, the cervical canal need not and should not be entered, but the presenting part may be felt easily and safely through the shortened cervical canal.

5. The entire examination is performed with one insertion of the examining finger. Multiple insertions serve only to increase the theoretical danger of introduction of infection.

6. If the cervix is posterior, all the necessary information can be obtained by palpation through the thinned lower uterine segment.

7. Following the examination the patient is warned of the possibility of slight vaginal bleeding.

#### Contraindications

Unsterile pelvic examinations are probably contraindicated in the presence of ruptured membranes. While the chance of causing genital tract infection is probably more theoretical than real, when the mem-

branes have ruptured there is a potential route for ascending infection.

A history of vaginal bleeding contraindicates office vaginal examination.

#### Results

During the past 5 years an estimated 6,000 office vaginal examinations were performed during the prenatal care of 2,000 consecutive obstetric patients. During this time there were no serious complications and no unfavorable results. The advantages gained have far outweighed the disadvantages. I am convinced that ninth month vaginal examinations and, for the sake of expediency, unsterile vaginal examinations have resulted in improved obstetric care and should be an integral and routine part of prenatal care.

#### Summary

No undesirable or serious complications were encountered in a series of approximately 6,000 unsterile antepartum vaginal examinations.

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## GYNECOLOGY

# An investigation of ovarian tissue and urinary 17-ketosteroids in patients with bilateral polycystic ovaries

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THE polycystic ovary was described in 1924 by Reynolds<sup>1</sup> who stated that "these ovaries tend to return to normal when tension on them is relaxed by operation." Stein and his associates<sup>2-4</sup> were the first to correlate polycystic ovaries with a clinical picture and to advocate wedge resection as one method of therapy.

Recently, there has been an increasing interest in polycystic ovaries, the Stein-Leventhal syndrome, and closely related conditions. Our experience on the Louisiana State University gynecology service at Charity Hospital in New Orleans has shown that increased physician awareness, the application of endocrine diagnostic techniques, and more exact clinical methods of diagnosis will disclose a greater number of such cases. Keettel and his associates<sup>5</sup> reported a similar

experience, and they stated that "the Stein-Leventhal syndrome was not diagnosed in our institution prior to 1952."

Delineation of exact etiological factors has been the subject of much investigation, and many theories have been advanced to explain this syndrome. Some previous research, considered by us to be most closely related to this problem, will be presented.

### Previous studies

**Morphological.** Alteration of arteriolar vascular patterns and increased intravascular pressure have been demonstrated in both the rabbit and human polycystic ovary.<sup>6,7</sup> Loss of ovarian arteriole spiraling may be due to abnormal hormone activity since similar vascular patterns in the functionalis layer of the endometrium have been found to be under hormonal control.<sup>8</sup>

**Hormonal-pituitary.** Hormonal participation in the development of follicular cysts has been demonstrated experimentally in humans. Administration of an anterior

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pituitary extract consisting largely of follicle-stimulating hormone resulted in the development of many cystic follicles with granulosa cell proliferation but without stromal fibrosis or theca luteinization.<sup>9</sup> Rapid increase of ovarian size in patients with the Stein-Leventhal syndrome after the administration of a pituitary follicle-stimulating hormone preparation was reported by Keettel and co-workers.<sup>5</sup> Qualitative assays for urinary luteinizing hormone indicated increased excretion in these patients. Determinations of urinary follicle-stimulating hormone excretion were found to be within normal limits by Ingersoll and McDermott<sup>10</sup> and Haas and Riley.<sup>11</sup>

**Adrenal.** The frequent observation of some degree of masculinization in these patients has often been attributed to excessive production of adrenal androgens. Mild to moderate elevation of total neutral urinary 17-ketosteroid excretion in patients with polycystic ovaries has been reported by many investigators.<sup>5, 12-21</sup> Following ovarian resection, some of these authors reported no change in the urinary 17-ketosteroid level, others a transient fall, and a few a permanent decrease.

More recently, detailed fractionation of urinary 17-ketosteroids in patients with the Stein-Leventhal syndrome has been done. Gallagher and his associates<sup>19</sup> demonstrated increased androsterone and etiocholanolone, with a slightly increased excretion of 11-oxysteroid metabolites in 4 patients. Carr and his co-workers<sup>20</sup> confirmed these findings for androsterone and etiocholanolone, but reported normal values for 11-oxysteroid excretion.

### Diagnosis

The gynecological histories of patients with the Stein-Leventhal syndrome usually follow a rather characteristic pattern. A normal menarche is followed by normal menstrual cycles which gradually become prolonged and irregular. The menstrual interval then increases until most patients exhibit amenorrhea, although some may continue to have only metropathia. Occa-

sionally, pregnancy occurs when coitus coincides with a rare ovulation, but most patients remain infertile. Obesity is reported, but the incidence is extremely variable. A more common finding is defeminization or masculinization with slight to moderate hirsutism being the most constant sign.

Although most of these patients have enlarged ovaries at laparotomy, only 40 to 50 per cent are diagnosed clinically. This discrepancy with ordinary pelvic examination may be due to obesity, poor relaxation, or the fact that nearly equal bilateral ovarian enlargement makes interpretation difficult. When ovarian visualization becomes necessary, laparotomy, colpotomy, culdoscopy, or gynecography may be employed. Gynecography was satisfactorily utilized in this study.

It has been reported that ovarian tissue may be capable of producing 17-ketosteroids,<sup>21-23</sup> however, in reviewing the literature, we were unable to find a report of ovarian tissue steroid determinations. It is the aim of this paper to present a study of 17-ketosteroid levels in the tissues of polycystic ovaries and in the tissues of ovaries which are grossly normal.

### Materials and methods

A study group of 19 patients with polycystic ovaries, and a control group of 5 young women were studied. The control group was to undergo vaginal hysterectomy for uterine prolapse. Preoperative evaluation of both groups included complete history and physical examination, routine hematological and urine studies, serum cholesterol determinations, endometrial biopsies, and total neutral urinary 17-ketosteroid determinations. Gynecography and postoperative urinary 17-ketosteroid determinations were performed only on the study group. Tissue resected from one ovary in 14 of the study patients and the grossly normal ovary from the control group were utilized for determination of 17-ketosteroid content. Tissue from the contralateral polycystic ovary was examined in the pathology laboratory.

All urine was collected from hospitalized patients in whom catheters had been placed,

Table I. Significant clinical data on the 19 study patients\*

Patient	G. B.	D. P.	V. J.	E. D.	S. H.	A. S.	M. S.
Age	23	22	20	20	24	21	21
Metropathia	+	+	+	-	+	-	+
Amenorrhea	-	+	+	+	+	+	-
Sterility	+	+	+	+	+	-	-
Habitus	O	O	O	O	O	O	N
Hirsutism	+	-	-	+	+	-	+
Clitoris	+	-	-	-	-	-	-
Ovaries on pelvic examination	N	N	N	N	N	+	N
Gynecography	+	+	+	+	+	+	+
Ovaries at operation	+	+	+	+	+	+	+
Preoperative endometrial biopsy	H	H	P	P	P	-	P
Postoperative endometrial biopsy	S	S	S	S	S	S	S
Bleeding postoperatively (hours)	24	48	48	24‡	48	72	24
Menstruation postoperatively	N	N	N	N	N	N	N
Follow-up (months)	22	18	15	14	12	12	12

\*N = normal; H = hyperplasia; P = proliferative; S = secretory; O = obese.

†Sisters.

‡Days.

and the greatest care was taken to insure adequate refrigeration. Determination of total neutral 17-ketosteroids was carried out by the method of Holtorff and Koch.<sup>24</sup>

Ovarian tissue 17-ketosteroid analysis was done after homogenization in the Waring blender for 15 minutes in 100 c.c. of distilled water. The extraction procedure was essentially that developed by Rohr and associates<sup>25</sup> and described by Keller and co-workers,<sup>25</sup> for adrenal tumors, except that  $\text{CCl}_4$  was substituted for benzene and the Zimmerman reaction applied to the  $\text{CCl}_4$  phase instead of Bush chromatography.

### Results

**Clinical findings.** The significant clinical data on the study patients are recorded in Table I. Table II lists the laboratory findings for both the study and the control groups. Vaginal bleeding occurred between 24 and 72 hours postoperatively in 15 of the 19 study patients. Three of the remaining 4 patients did not have this rapid onset of vaginal bleeding (V. G., E. D., and J. K.). The fourth patient (M. W.) has remained amenorrheic since operation unless

progesterone therapy is used. Therefore, 18 of the 19 patients (94.7 per cent) have reverted to and have continued to maintain normal menstrual periods postoperatively. Follow-up has been as long as 22 months.

Twelve patients were infertile; 6 were single, and one had one child and did not desire pregnancy at this time. Some degree of obesity was noted in 12 patients; 14 exhibited hirsutism, and 5 had slight enlargement of the clitoris.

Gynecography showed bilateral ovarian enlargement in 18 patients and ovaries of normal size in only one. The results of gynecography were confirmed at the time of operation. Ovarian enlargement was described in only 5 patients with ordinary pelvic examination (27.3 per cent).

**Urinary steroids.** The established normal range for total neutral urinary 17-ketosteroids in our laboratory is 5 to 15 mg. per 24 hours. The control group averaged 15.3 mg. per 24 hours, while the mean of the study group was 23.5 mg. per 24 hours. This difference of 8.2 mg. per 24 hours between the study and control groups is not statistically significant ( $P > 0.1-0.2$ ).

	S. M.	D. R.	L. W.	I. T.	V. G.	E. F.	M. H.	G. M.	M. W.	B. T.†	E. S.†	J. K.
21	18	28	28	19	21	27	17	18	33	30	21	21
+	+	+	+	+	+	-	+	-	-	-	-	+
-	+	+	-	+	-	+	+	+	+	+	+	-
N	-	-	+	+	-	-	-	+	+	+	+	+
+	N	N	O	O	O	N	N	O	O	N	N	O
-	+	+	+	+	-	+	+	+	+	+	+	-
	-	+	+	-	-	+	-	-	-	-	-	+
N	N	+	N	+	N	+	N	N	N	+	N	N
+	+	+	+	+	+	+	+	+	N	+	+	+
+	+	+	+	+	+	+	+	+	N	+	+	+
P	H	P	P	P	H	H	-	P	H	P	H	H
S	S	S	S	S	P	S	S	P	P	S	S	S
24	48	48	72	48	75‡	24	48	48	-	24	72	30‡
N	N	N	N	N	N	N	N	N	-	N	N	N
12	12	11	10	10	10	9	9	9	7	6	6	6

Urinary 17-ketosteroid determinations 6 weeks postoperatively disclosed a lowered excretion in all patients in the study group. The average decrease was 11.4 mg. per 24 hours, which is statistically significant ( $p < .001$ ).

**Ovarian tissue steroids.** Tissue 17-ketosteroids of the study group varied between 1.2 and 8.6  $\mu\text{g}$  per gram, averaging 4.5  $\mu\text{g}$  per gram. Ovarian tissue excised for assay from the study group weighed 1.5 to 15 grams.

Ovarian weight in the control group was 4.6 to 8.2 grams and tissue 17-ketosteroids averaged 4.0  $\mu\text{g}$  per gram, with a range of 1.9 to 7.8  $\mu\text{g}$  per gram.

There was no correlation between ovarian size, amount of tissue resected, ovarian tissue steroid content, microscopic pathology, and the pre- and postoperative urinary 17-ketosteroid excretion.

**Comment**

Variable laboratory and clinical findings make difficult a clear understanding of the Stein-Leventhal syndrome. Further confusion is brought about by the fact that sev-

eral different surgical procedures alleviate this condition. Thus, wedge resection of both cortical and stromal tissue,<sup>2-4</sup> resection of only medullary tissue,<sup>26</sup> or partial removal of the thickened capsule<sup>27</sup> per se seem to give satisfactory results. While many theories of causation for the Stein-Leventhal syndrome have been advanced, the following possibilities, divided into three main categories, seem most logical:

- 1. Changes within the ovary
  - a. Anatomic (ovulatory interference)
  - b. Androgen production
- 2. Pituitary gonadotrophin imbalance
  - a. Excessive production of luteinizing hormone
- 3. Abnormal adrenal cortical metabolism
  - a. Primary
  - b. Secondary to:
    - (1) Pituitary dysfunction (? ACTH increase)
    - (2) Ovarian dysfunction (androgen production or secretion of an unknown factor)

Stein<sup>4</sup> has reported symptomatic cures for many years following wedge resection. Such successful long-term effect points to the

strong possibility that there is a primary defect in the ovary itself. It hardly seems logical that such permanent success would occur if the fundamental pathology lay within the adrenal gland or pituitary gland.

This investigation was carried out in order to establish whether or not the increased urinary excretion of neutral 17-ketosteroids, which often disappears after ovarian wedge resection, is due to the fact that the ovary itself secretes these substances. We have found that the ovary does not contain increased amounts of these hormones, and therefore we must come to the conclusion that the ovary is not the site of production of the increased neutral 17-ketosteroids which are excreted in the urine of these patients. The elimination of this possibility undoubtedly weakens the ovarian theory and seems to point to the probability that the adrenal cortex is the more likely site of causation. The recent work of Gallagher<sup>16</sup> and

Carr<sup>20</sup> and their associates, showing an increase of 17-ketosteroid fractions as well as 11-oxysteroid metabolites, tends to substantiate this, as does the clinical fact that the administration of cortisone may cause clinical improvement, ovulation, and pregnancy. The latter is presumed to be on the basis of pituitary depression, lessened ACTH secretion, and subsequent reduction of adrenal cortical activity.

On the other hand, there is scientific data which tends to cast some doubt upon such a simple explanation. The administration of ACTH has not been shown capable either of developing or of worsening this disease. In fact, Carr and co-workers<sup>20</sup> have demonstrated a decreased response to the administration of ACTH in these patients. Therefore, an ovarian factor cannot be ruled out, and it is quite possible that such may function to stimulate the adrenal androgen biosynthetic pathways.

Table II. Significant laboratory data on study and control groups

Patient	Age	Urinary 17-ketosteroids		Ovarian tissue (micrograms per gram)	Grams of tissue
		Preoperative (mg./24 hr.)	Postoperative (mg./24 hr.)		
Study group					
G. B.	23	23	12	—	—
D. P.	22	42	12	—	—
V. J.	20	17	6	—	—
E. D.	20	23	14	—	—
S. H.	24	20	11	—	—
A. S.	21	43	11	7.4	6.8
M. S.	21	21	14	2.1	7.5
S. M.	18	22	10	1.2	2.8
D. R.	28	22	9	2.3	14.0
L. W.	28	21	18	1.8	3.8
I. T.	19	26	9	2.7	15.0
V. G.	21	20	16	8.6	2.4
E. F.	27	23	13	1.6	9.4
M. H.	17	41	8	5.8	9.8
G. M.	18	20	16	2.9	9.0
M. W.	33	16	9	2.2	1.5
B. T.	30	20	12	8.1	12.0
E. S.	21	8	5	8.6	7.0
J. K.	21	19	13	8.4	2.0
Average	22.7	23.5	11.4	4.5	7.3
Control group					
G. S.	32	12	—	1.9	7.0
N. M.	33	15	—	2.2	4.6
E. W.	33	15	—	2.1	6.0
E. R.	30	19	—	5.8	8.2
G. L.	30	15	—	7.8	6.6
Average	31.6	15.3	—	4.0	6.5



It is obvious that further fundamental work needs to be done before we can completely understand this interesting condition. It is hoped that this investigation may help point the way to the ultimate solution.

### Summary

1. Total neutral urinary 17-ketosteroids were found to be elevated in patients with bilateral polycystic ovaries.

2. Following ovarian wedge resection, there was a statistically significant decrease of these elevated steroids.

3. No significant difference of ovarian tissue 17-ketosteroid levels was found between the study and control groups.

4. It must be concluded from this study that the ovary does not produce the increased urinary 17-ketosteroids found in these patients.

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# Clinical and laboratory effects of nortestosterone

## I. The management of anovulatory dysfunctional uterine bleeding

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THE use of intermittent progesterone administration to control the irregular or heavy bleeding of anovulatory cycles has been well established.<sup>1</sup> Progesterone converts proliferative or hyperplastic endometrium to a secretory stage and after withdrawal of the progesterone an essentially normal menstrual flow ensues. The periodic administration of progesterone prevents the uninterrupted growth of the endometrium and the resultant hemorrhages or prolonged bleeding that occurs from either proliferative or hyperplastic endometrium.

It has also been claimed that the repeated administration of progesterone is followed by spontaneous ovulatory cycles.<sup>1</sup> Its efficacy in this regard is not so well established. Whether any such ovulations are due to the therapeutic effects of progesterone or are merely the results of a spontaneous remission remains a debatable subject and one that is not within the province of this presentation.

We agree that progesterone has a definite place in the management of the irregular and heavy bleeding of anovulatory cycles. It is the purpose of this paper to present our experience with the use of two highly progestational synthetic steroids, 17-alpha-ethinyl-19-nortestosterone (Norlutin) and 17-alpha-methyl-19-nortestosterone (Methalutin) in the control of anovulatory cycles.

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*Supported by a grant from the Population Council.*

### Historical

In 1954 Hertz<sup>2</sup> reported that replacement of the methyl group at carbon-10 of the testosterone molecule with hydrogen resulted in compounds with at least five times the progestational activity of pregneninolone as judged by the effect on the endometrium. Of additional significance was the fact that these compounds lost none of their potency when administered by the oral route, a characteristic unfortunately not shared by progesterone itself.

These compounds are known as nortestosterones. A number of such steroids have been synthesized. 17-alpha-ethinyl-19-nortestosterone (Norlutin) has been extensively studied in both animals and humans. Changes in the endometrium of human castrates and amenorrheic subjects have been described varying from marked secretory changes in the glands to profound decidual reaction in the stroma. These changes have occurred when the compounds have been administered in dosages of 10 to 25 mg. for periods ranging from 14 to 25 days.<sup>3-5</sup> Southam<sup>6</sup> reported that 5 mg. of 17-alpha-ethinyl-19-nortestosterone given daily for 14 days will produce withdrawal flow in amenorrheic subjects.

Fewer observations have been reported utilizing 17-alpha-methyl-19-nortestosterone (Methalutin) and also less experience has been reported utilizing smaller dosage levels. Ferin<sup>7</sup> has described secretory changes in the endometrium when both Norlutin and Methalutin were given in dosages as low as 2 mg. daily for 8 days. Early secretory

changes were noted with 17-alpha-methyl-19-nortestosterone when as little as 5 mg. was given for 4 days.<sup>8</sup> The sublingual route of administration was utilized.

Since these compounds have been shown to be such potent progestational agents and since they appear capable of producing secretory changes in the proliferative endometrium at extremely low dosages, we felt that 2 mg. daily by the oral route over a 4 day period should be sufficient to halt the continued proliferation of the endometrium of anovulatory cycles and allow for satisfactory control.

#### Material and methods

Clinic and private patients with the diagnosis of dysfunctional uterine bleeding due to anovulation were followed and treated when amenorrhea had been present for a minimum of 5 weeks.

The diagnosis of anovulation was made by curettage or endometrial biopsy just prior to uterine bleeding in the older patients or by pregnanediol determination or basal body temperature charts in younger subjects.

Whenever possible, a fern test was performed on the cervical mucus just prior to the administration of the course of steroids.

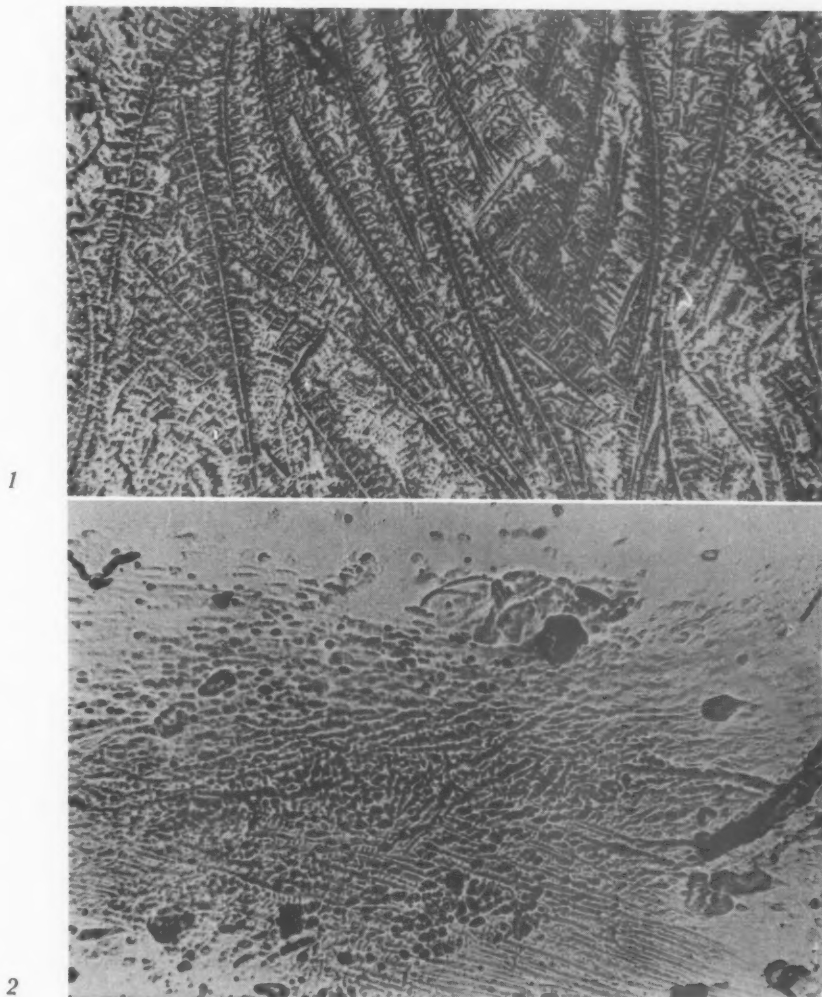


Fig. 1. Three-plus ferning of cervical mucus indicative of adequate estrogen level.

Fig. 2. One-plus ferning of cervical mucus indicative of low estrogen level or progesterone secretion.

By our standards<sup>9</sup> good ferning (2 or 3 plus) of the cervical mucus is an indication of a good estrogen level without progesterone (Fig. 1).

Conversely, absent or poor ferning (0 or 1 plus) indicates that either a low estrogen level is present or that progesterone is being secreted (Fig. 2). One would not expect a withdrawal flow after the administration of a progestational compound to a subject with poor ferning. Indeed, under such circumstances there is no indication for the administration of progesterone.

If the fern test was positive, nortestosterone in dosages ranging from 1.25 to 3 mg. was administered daily for 4 days. A number of patients were given sufficient medication for repeat courses to be administered at home when they had gone 5 weeks without another menstrual flow.

Results

The results are shown in Table I. Amenorrhea varied from 35 days to 2 years in duration. 17-Alpha-methyl-19-nortestosterone was given in 21 cycles to 16 patients. Withdrawal flow occurred in all but 2 patients within one to 6 days after cessation of the medication. These 2 patients probably represent ovulation occurring close to the time of administration of the medication. In 16 of the remaining 19 cycles withdrawal flow began within 3 days of the cessation of medication.

Many of the cycles do not have a fern test associated with the administration of nortestosterone either because they had been given progesterone intramuscularly on the initial office visit and the nortestosterone was taken at home when the period was again overdue or because some of the cycles represent repeated self-administration at home when the period was overdue.

In order to demonstrate the effect of this level of nortestosterone on an estrogen-primed endometrium 2 mg. of 17-alpha-methyl-19-nortestosterone daily for 4 days was given to a patient known to have x-ray castration, whose endometrium had previously been primed with estrogen. An

endometrial biopsy was performed on the fourth day of 17-alpha-methyl-19-nortestosterone administration. A pregnanediol test was also performed on this day to rule out an intrinsic source of progesterone, and this was found to be negative. Edema of the stroma and basal vacuolization similar to that seen in the early secretory phase are easily visible in Fig. 3.

A similar clinical result was noted when 17-alpha-ethinyl-19-nortestosterone in doses of 2.5 mg. daily for 4 days was given to 6 patients (Table I), although the onset of the withdrawal flow seemed somewhat delayed.

Case 10 (Table I) demonstrates the results of self-medication at 5 week intervals in the control of the irregular cycles of

Table I. Nortestosterone in anovulatory cycles

Case No.	Duration of amenorrhea (days)	Fern	Dosages	Onset of flow (days later)
Methalutin				
1	35	3 plus	3 mg. 4 times	1
2	57	3 plus	2 mg. 4 times	2
3	41		2 mg. 4 times	2
4	66	3 plus	2 mg. 4 times	2
	70	3 plus	2 mg. 4 times	13*
5	67		2 mg. 4 times	2
	50		2 mg. 4 times	2
6	43	3 plus	2 mg. 4 times	1
7	43	3 plus	2 mg. 4 times	3
	92	2 plus	2 mg. 4 times	2
8	2 years		2 mg. 4 times	1
9	34		2 mg. 4 times	5
10	47		2 mg. 4 times	1
	35		2 mg. 4 times	2
	35		2 mg. 4 times	1
11	56	3 plus	2 mg. 4 times	5
12	54	3 plus	2 mg. 4 times	
13	35		2 mg. 4 times	17*
14	50		2 mg. 4 times	3
15	35		2 mg. 4 times	3
16	67		1.25 mg. 4 times	2
Norlutin				
17	38		2.5 mg. 4 times	1
18	52	3 plus	2.5 mg. 4 times	7
19	35		2.5 mg. 4 times	3
20	93	2 plus	2.5 mg. 4 times	2
21	60	3 plus	2.5 mg. 4 times	4
22	56	3 plus	2.5 mg. 4 times	7

\*Escape.





Fig. 3. Endometrial biopsy in x-ray castrated woman after priming with estrogen and after 4 days of Methalutin, 2 mg. per day.

anovulatory bleeding. The patient, age 19, had been seen over the past few years because of intermittent episodes of amenorrhea followed by prolonged and heavy bleeding. This had been treated at times with intramuscular injections of progesterone. When seen again during the course of this study she had been amenorrheic for 2 months. She was given 17-alpha-methyl-19-nortestosterone, 2 mg. daily for 4 days, and sufficient medication to take similar dosages at home when her period was overdue during the next few months. A menstrual flow promptly occurred at the cessation of the initial course of therapy and when the medication had been taken again over the next 2 months when the patient's period was one week overdue.

No side effects were noted. 17-Alpha-methyl-19-nortestosterone is known to have androgenic properties equivalent to methyltestosterone, but any effect at this minimal dose level would be negligible.

#### Summary and conclusions

Small dosages of nortestosterone by mouth have been shown to be capable of converting an estrogen-primed endometrium into a secretory pattern, and withdrawal flow occurs promptly after cessation of the medication.

This should provide a convenient and relatively inexpensive method of preventing the irregular and heavy uterine bleeding often associated with anovulatory menstrual bleeding.

Oral medication, allowing for self-administration at home at prescribed intervals, is more convenient for both the patient and the doctor.

The use of this program should reduce the number of surgical curettages sometimes necessary in adolescence to control hemorrhage or prolonged flow. Often, with physical or emotional maturity, spontaneous remissions occur and future therapy is no longer needed. The bleeding of premenopausal patients, too, can be controlled temporarily until menstrual function ceases altogether, and hysterectomy can in many instances be avoided.

No side effects have been noted at this small dosage level.

We are indebted to Dr. E. J. Gajewski of Parke, Davis & Company for a supply of Norlutin and to Syntex, S. A., for Methalutin.

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# Tumors of the gonads in cases of gonadal dysgenesis and male pseudohermaphroditism

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LAPAROTOMY in cases of primary amenorrhea and sexual immaturity with defective somatic development (e.g., eunuchoidism and Turner's syndrome) may reveal gonadal tumors, the presence of which was not suspected before operation. These tumors may be of malignant embryonal nature. This is a most important argument in favor of performing exploratory laparotomy in each case of primary amenorrhea and somatosexual disturbance.

This problem has not been much reviewed in the literature, although it is not a new one. As early as 1900, Neugebauer,<sup>5</sup> a gynecologist from Warsaw, in one of his numerous works on hermaphroditism and genetic disturbances, described 19 cases of benign and malignant genital tumors which had developed in hermaphrodites.

In 1931, Robert Meyer<sup>4</sup> described 2 cases with dysgerminoma of one ovary and a rudimentary gonad on the contralateral side. Moreover, he described one case of gonadal aplasia on one side while on the other side was found "a tumor composed of epithelioid cells." In 1953, Morris<sup>3</sup> collected from the world literature data on 92 cases of male pseudohermaphroditism in the form of a so-called testicular feminization syndrome, and in 7 cases he demonstrated

the existence of malignant tumors in underdeveloped male gonads.

In 1957, Stange<sup>12</sup> described 4 cases of tumors which had been found at laparotomy among 15 cases of gonadal dysgenesis. In one case he found a Brenner tumor; in 2 cases, hilus cell tumors; and in the fourth, an exuberance of rete testis elements.

The object of this report is to describe 4 cases of tumors revealed by exploratory laparotomy performed because of primary amenorrhea and disturbances in somatic development. These cases were found to represent gonadal dysgenesis or male pseudohermaphroditism. The tumors presented interesting and rare forms. In one case there was a gonadoblastoma; in 2 cases, dysgerminoma or seminoma; and in one case, adenoma of the hilus cells. The fact that these 4 tumors were discovered among a group of only 13 cases of somatosexual disturbances and gonadal dysgenesis seems significant.

## Material

During 1956 and 1957, exploratory laparotomy was performed in 13 cases of gonadal dysgenesis and disturbances of somatosexual development. All of these patients had been registered as women. Their external female genitals showed various degrees of infantilism and underdevelopment. In all these cases the gonadotropin titer was elevated. The somatic structure of 6 patients was eunuchoidal, 4 were of the classic Turner dwarf type, and 2 resembled the Turner type (Table I).

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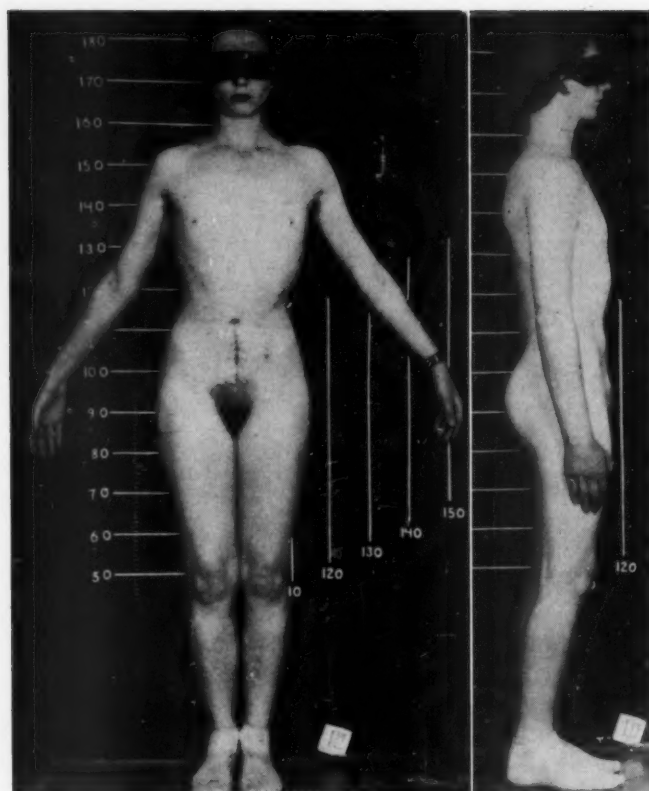


Fig. 1. Case 1. Gonadal dysgenesis and male pseudohermaphroditism. Note eunuchoidal body build.

In 8 cases, determinations of genetic sex revealed genetic males. Among these individuals 7 showed female psychosexual tendencies and only one showed male tendencies. All the patients were examined by gynecologists because of an initial diagnosis of "primary amenorrhea." In order to render more precise diagnoses, laparotomy was advised in each case.

#### Case reports

**Case 1.** T. J. (4658), a 26-year-old patient, had been reared as a girl but she considered herself a man and had clitoral erections. Since the age of 12 she had had a strong libido for girls. At first she practiced onanism and later she had sexual intercourse as a "boy." She wished to change her sex and for this purpose she visited the urological clinic, where laparotomy was decided upon.

The body build was eunuchoidal, with broad flat chest, breast aplasia, and female hair (Fig. 1). Height was 182 cm. and arm span 192 cm.

Gynecological examination revealed a clitoris resembling a penis, 6 cm. long with glans and prepuce. The opening of the urethra was situ-

ated under the clitoris. Below there were a vestibule, labia majora and minora, and a small rudimentary vagina about 3 or 4 cm. long. The titer of gonadotropins was above 200 and below 300 international units. The genetic sex was male.

Laparotomy revealed the presence of a small, correctly formed uterus and oviducts with fimbriae. On the left side, in the position normally occupied by the ovary, a rudimentary ridge-shaped gonad, 2 cm. long and 0.5 cm. in diameter, was found. A specimen was taken from this rudimentary gonad. On the right side, in the usual position of the ovary, there was an oval formation about 5 cm. in diameter, the size of a hen's egg. This was removed.

**Microscopic study of the gonads.** The rudimentary gonad was composed of a cortical zone similar to the connective tissue stroma of an ovary (Fig. 2) and an underdeveloped medullary zone without interstitial cells. There were no seminiferous tubules or follicles. The gonad was entirely sterile. In its deeper layers some tubules of mesonephric origin were identified.

Section of the right gonad revealed numerous nests of round or oval cells with large, bright,

Fig. 2. Microscopic picture of the rudimentary gonad. The ovary is underdeveloped and contains no follicles or seminiferous tubules.

Fig. 3. Microscopic picture of the right gonad. The gonad is composed of a cortical zone and an underdeveloped medullary zone.

foamy cells. These cells are arranged in nests and are surrounded by connective tissue. The gonad is entirely sterile.

Case 2. A 26-year-old patient, T. J. (4659), had been reared as a girl but she considered herself a man and had clitoral erections. Since the age of 12 she had had a strong libido for girls. At first she practiced onanism and later she had sexual intercourse as a "boy." She wished to change her sex and for this purpose she visited the urological clinic, where laparotomy was decided upon.



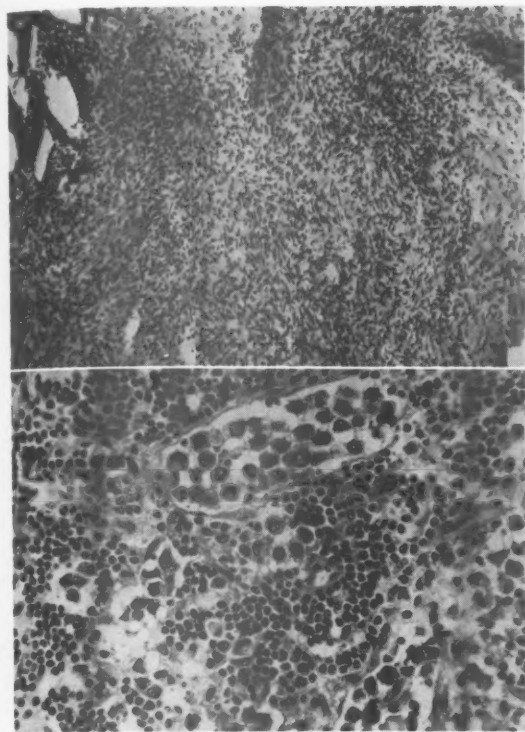


Fig. 2. Case 1. The left gonad. The histological picture shows the cortical zone, which resembles ovarian stroma, and the medullary zone, which is underdeveloped and contains neither Leydig nor hilus cell elements. In the upper left are some tubules of mesonephric origin.

Fig. 3. Case 1. Tumor of the right gonad. Photomicrograph presenting the typical appearance of a dysgerminoma. The dysgerminal cells are arranged in irregular, oval nests, separated by a well-defined fibrous stroma heavily infiltrated with lymphocytes.

foamy cytoplasm and large nuclei which contained delicate chromatin and distinct nucleoli. These cells were recognized as germ cells. Between the nests of tumor cells there were small strands of connective tissue stroma with hyalinization and lymphocytic infiltration. The general structure of the tumor was alveolarlike although there were areas of disorderly massed cells and occasional islands (Fig. 3). Dysgerminoma (or seminoma) was diagnosed.

**Case 2.** S. J. (1095), aged 33, manifested primary amenorrhea, delayed puberty, and eunuchoidism. The psychosexual make-up was female, as were the social sex and appearance (Fig. 4). Height was 163 cm.; arm span, 173 cm.; weight, 65 kilograms. The breasts were underdeveloped and in the pubescent stage.

Puboaillary hair was scant. The chromosomal sex was female. Urinary gonadotropins were above 200 and below 300 international units; the urinary 17-ketosteroids were 8.8 mg.

Laparotomy revealed an infantile uterus and oviducts. On the left side there was a rudimentary gonad of an oblong, wormlike, whitish appearance, 3 cm. in length and 0.5 cm. in diameter. On the right side there was a knobby mass resembling an ovary and measuring 4 by 1.5 by 1 cm. (Fig. 5). Bilateral salpingo-oophorectomy was performed.

*Microscopic study of the gonads.* Microscopic study of the left gonad revealed a cortical zone of tissue resembling ovarian connective tissue stroma. There were no primordial cells. The medullary zone was underdeveloped. In the hilar area were large nests of interstitial cells resembling theca-lutein cells. Some groups of typical hilus cells were arranged concentrically around nonmyelinated nerves. In the deeper layers were numerous tubules thought to represent remnants of mesonephros.

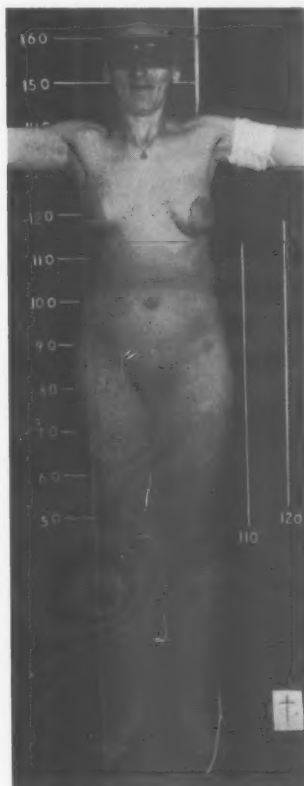


Fig. 4. Case 2. Eunuchoidism with primary amenorrhea. Note underdeveloped breasts and scant body hair.

Table I. Exploratory laparotomy in 13 cases of gonadal dysgenesis (characteristics of patients)

Case no.	Age and record no.	Legal sex	Psycho-sexual orientation	Sex chromatin	Habitus	Hair	External genitals				Uterus	Gonads	
							Clitoris	Labia	Vagina	Left		Right	
1	22 (3752)	♀	♀	♂	Eunuchoidal	Absent	Infantile	Infantile	Infantile	Rudimentary	Rudimentary	Rudimentary	
2	37 (2771)	♀	♀	♂	Eunuchoidal	Scanty	Hypertrophied	Normal	Infantile	Infantile	Dysgenetic	Dysgenetic	
3	31 (2011)	♀	♀	♂	Eunuchoidal with masculinization	Normal	Penile	Hypertrophied	Infantile	Infantile	Dysgenetic with rudimentary tubules; seminiferous; Leydig cells	Leydig cells	
4	19 (6286)	♀	♀	♂	Turner	Scanty	Well-developed	Infantile	Infantile	Fetal	Adenoma of hilus cells; immature seminiferous tubules	Dysgenetic	
5	23 (6360)	♀	♀	♂	Turner	Absent	Infantile	Infantile	Infantile	Fetal	Rudimentary	Rudimentary	
6	27 (6877)	♀	♀	♂	Turner	Absent	Infantile	Infantile	Infantile	Rudimentary	Rudimentary	Rudimentary	
7	17 (5365)	♀	♀	♀	Turner	Absent	Infantile	Infantile	Infantile	Fetal	Dysgenetic	Dysgenetic	
8	26 (4658)	♀	♂	♂	Eunuchoidal with masculinization	Normal	Penile	Infantile	Rudimentary	Fetal	Rudimentary	Dysgerminoma (seminoma)	
9	29 (6394)	♀	♀	♀	Eunuchoidal	Absent	Infantile	Infantile	Infantile	Fetal	Rudimentary	Rudimentary	
10	19 (1095)	♀	♀	♀	Eunuchoidal with female appearance	Scanty	Infantile	Normal	Normal	Infantile	Rudimentary	Dysgerminoma	
11	19 (4399)	♀	♀	♀	Slender girl	Absent	Infantile	Infantile	Infantile	Fetal	Rudimentary	Rudimentary	
12	31 (6862)	♀	♀	♀	Turner with quasi-normal female body proportions	Scanty	Infantile	Infantile	Infantile	Infantile	Rudimentary	Rudimentary	
13	19 (5594)	♀	♀	♂	Turner with boy's appearance	Normal	Penile	Scrotal	Infantile	Infantile	Dysgenetic with immature seminiferous tubules	Gonadoblastoma	

Fig. 5  
Case 1

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The female thighs was en covered The la pearan finger; the th smaller was a which

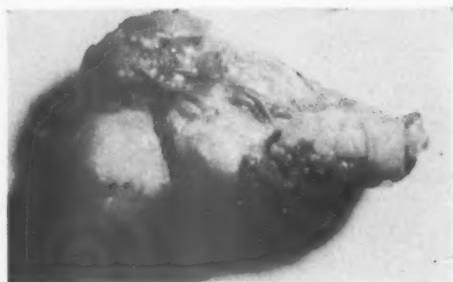


Fig. 5. The small tumor of the right gonad in Case 2.

The right gonad contained large nests of round or oval cells with bright cytoplasm containing large, round, centrally situated nuclei. These nuclei contained big clumps of chromatin. Between the cell nests there were connective tissue strands with lymphocytic infiltration and signs of hyalinization (Figs. 6 and 7). In some connective tissue areas large calcified flecks could be seen. The tumor was recognized as a dysgerminoma. In some parts of the tumor the groups of dysgerminoma cells were separated by dark syncytial giant cells resembling syncytial trophoblast. It should be emphasized that the pattern of these parts of the tumor resembled choriocarcinoma.

**Case 3.** C. A. (5594), a 19-year-old, had undergone mutation of the voice 6 years previously. Psychosexual tendencies were definitely female. She "felt right" in the society of boys and superficial sexual intercourse gave her great satisfaction.

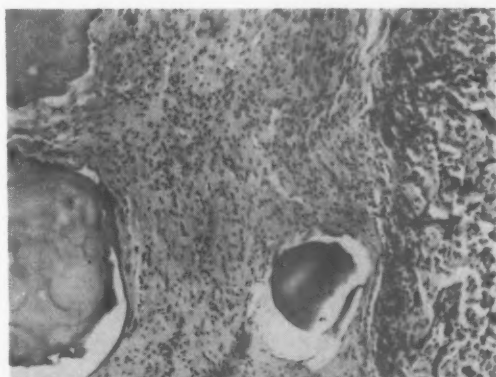
The physical appearance was that of a boy. Weight was 41.7 kilograms; height, 146 cm.; span of shoulders, 159 cm.; circumference of chest, 76 cm.; bitrochanteric measurement, 35 cm. A male morphotype. There was no facial or axillary hair. The breasts were in an early stage of development (adolescent type) (Fig. 8).

The pubic hair resembled that of an adult female. It spread to the medial surface of the thighs but not up the linea alba. The clitoris was enlarged, measuring 4 by 1.5 cm., and was covered by a large preputial fold with smegma. The labia were hypertrophied with a scrotal appearance. The vagina was narrow, admitting one finger; its walls were smooth. The cervix was the thickness of a pencil. The fundus uteri was smaller than a cherry. The axis of the fundus was a prolongation of the axis of the cervix, which is typical of uterus fetalis. The left gonad

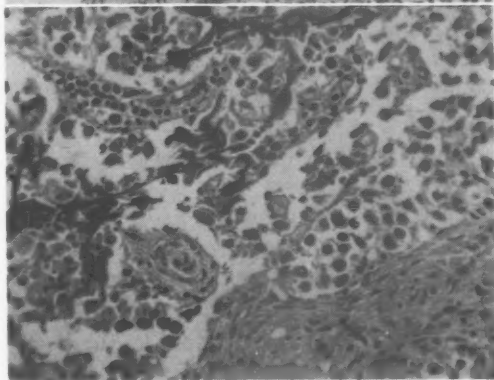
was not palpable. The right gonad was enlarged to the size of a walnut and was round and very compact. The chromosomal pattern was male. 17-Ketosteroid urinary assays varied from 5.0 to 7.3 mg. per day. Gonadotropin assay was above 100 and less than 200 international units.

On the basis of these assays the diagnosis was "intermediate form between gonadal dysgenesis and the classic varieties of male pseudohermaphroditism."

At laparotomy the uterus and Fallopian tubes were found to be infantile. On the posterior surface of the left broad ligament in the location normally occupied by the ovary, a tumor was found which measured 5.5 by 4.5 by 3.5 cm. Its surface was smooth and shiny. On section the neoplastic tissue was found to be firm and lobulated. On its surface millet-sized calcific foci were palpable. A bilateral salpingo-oophorectomy was performed.



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Fig. 6. Case 2. Dysgerminoma of the right ovary. Right: nest of dysgerminoma cells; center: the connective tissue with hyalinization and an area of calcification.

Fig. 7. Case 2. High-power view of the dysgerminoma cells surrounded by a hyalinized lymphoid stroma.

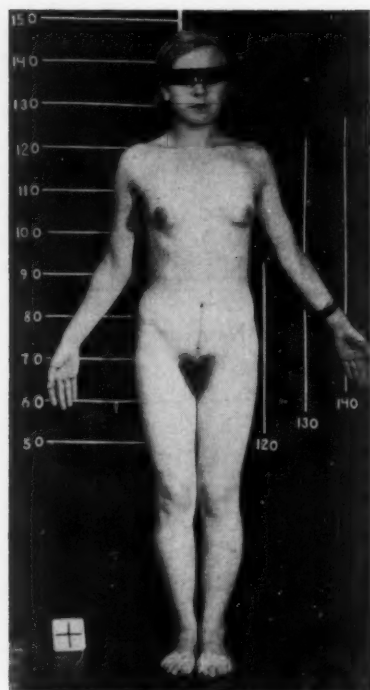


Fig. 8. Case 3. A case of primary amenorrhea. Note boyish figure and underdeveloped breasts.

*Microscopic study of the gonads.* Histologically, the cortex of the left gonad resembled the connective tissue stroma of the ovary. In the medullary region there were a few scattered clusters of sex-cord type cells and germ cells. The sex-cord type cells were arranged in folliculoid groups and in formations resembling rudimentary fetal seminal tubules with evidence of degeneration by hyalinization.

The pathological findings in the tumor of the right gonad were as follows: the capsule of the tumor was composed of fibrous tissue resembling ovarian stroma; the neoplastic tissue was lobulated and composed of an area of dysgerminoma cells arranged in round or oval nests with scanty lymphoid stroma. In the entire area, germ cell elements were mixed with Sertoli or granulosa cells (Figs. 9-12).

In the region of the neoplastic nests the stroma was composed of a dense collagenous material with scattered calcific foci. The stroma was composed of large sheets of cells morphologically resembling Leydig or theca-lutein cells. In addition to this, the stroma contained calcific foci. This histological picture satisfied the morphological criteria given by Scully<sup>8</sup> for the "gonadoblastoma" tumor.

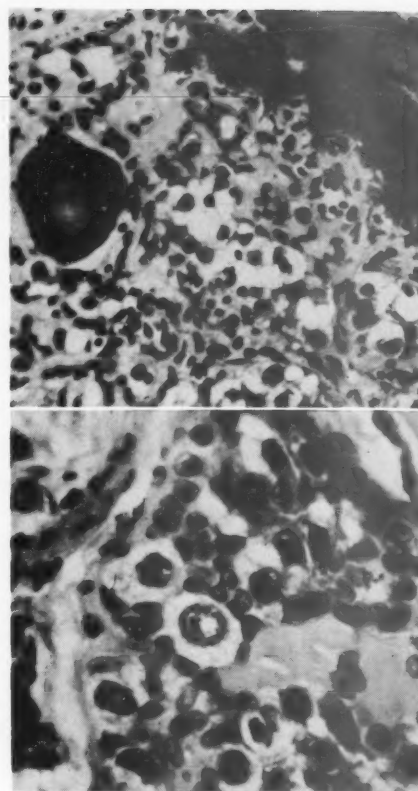


Fig. 9. Case 3. Gonadoblastoma of the right gonad. The tumor cell mass is composed of a mixture of dysgerminoma cells and sex-cord type cells (Sertoli or granulosa cells). Note the calcified concretion surrounded by hyalinized connective tissue.

Fig. 10. Case 3. High-power view of the tumor cell nests. The small cells with oval, bent nuclei are the sex-cord type cells (Sertoli or granulosa cells) arranged in coronal fashion about individual germ cells.

**Case 4.** M. J. (6286) was 19 years old with female psychosexual orientation. She was only 140 cm. tall. The legs were heavy; the neck was short but without webbing. She had a round face, "barrel chest," infantile, widely spaced nipples and protuberant abdomen (Fig. 13).

The pubic hair was only 40 per cent of normal. The labia majora were underdeveloped and slightly pigmented. There was a quite well-developed clitoris, resembling a normal one. The vagina was narrow and 8 cm. long. The chromosomal sex pattern was male; the 17-ketosteroids, 4.9 mg. per 24 hours.

At laparotomy a rather small fetal uterus was found with long, thin tubes. The right gonad was 3 cm. long and 2 mm. thick; the left one, 4

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Fig. 11 showing cord about ments cells Fig. 12 nest. in a germi

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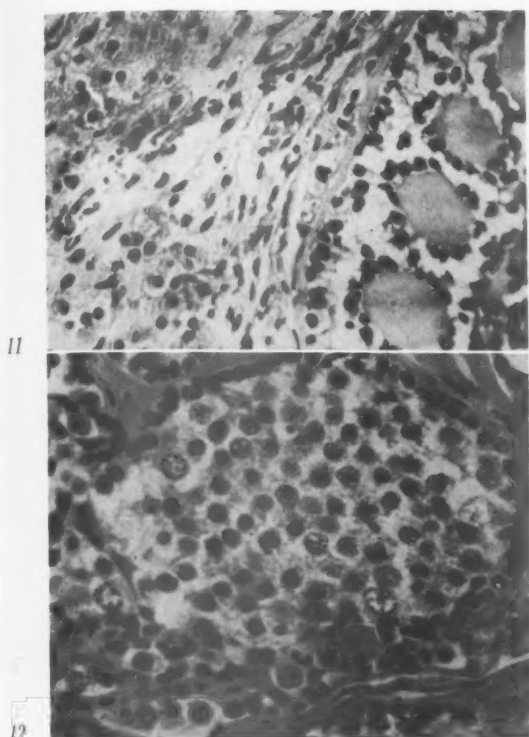


Fig. 11. Case 3. Another section of the tumor showing a mixture of 3 types of cells: (1) sex-cord cells (right) arranged in folliculoid pattern about individual germ cells, (2) mesenchymal elements (interstitial cells) in the center, and (3) cells of the Leydig or theca-lutein type (left).  
Fig. 12. Case 3. High-power view of a tumor cell nest. The small sex-cord type cells are arranged in a single peripheral layer surrounding the dysgerminoma cells.

cm. long and 4 mm. thick in the form of a whitish ridge.

*Microscopic study of the gonads.* Examination of the right gonad revealed a fairly well-developed cortical zone, similar to ovarian stroma and containing spindle-shaped connective tissue elements arranged in whorls. In the medullary area there were no seminiferous tubules and only 3 rete tubules. Within the area of this hilus, several polygonal epithelioid cells, which resembled theca-lutein cells, were found.

The cortex of the left gonad was narrow and relatively acellular. In the medullary part, a concentration of mesenchymal cells was found with some germ cells among them. These cells were arranged in cords and formed tubules similar to immature seminiferous tubules of the fetal testis.

Further sections of the hilar area revealed a large focus of hilus cells surrounding the non-



Fig. 13. Case 4. A case of primary amenorrhea. Note the underdeveloped appearance of this 19-year-old.

myelinated nerves. The cells were arranged in mosaic fashion. Most of them had oval, centrally situated nuclei and an abundant eosinophilic, slightly granular cytoplasm. This was regarded as an adenoma of hilus cells (Fig. 14).

#### Comment

Such a high incidence of tumors (33 per cent) among 13 cases of gonadal dysgenesis merits attention. There were 3 embryonic tumors (gonadoblastoma in one and dysgerminoma in 2) and one hilus cell adenoma. There seems to be no doubt that a thorough histological study of gonads in these cases of somatosexual disturbance is likely to reveal a significant number of anomalies and tumors.<sup>3, 5, 12</sup> It should be strongly emphasized that in none of the cases which have been described did we suspect the presence of a gonadal tumor before laparotomy. In each of these cases the detection of a tumor was a surprise to us.

In addition to symptoms of gonadal dysgenesis, 2 of our cases, Nos. 1 and 3, presented characteristics of male pseudohermaphroditism. In cases of pseudohermaph-

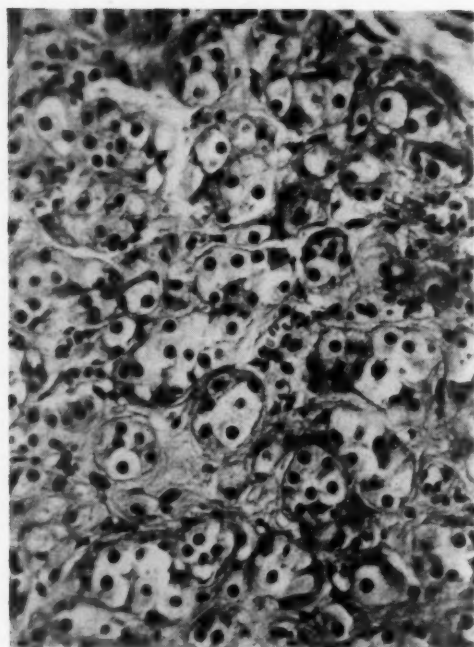


Fig. 14. Case 4. Adenoma of hilus cells in the rudimentary left gonad. The tumor is composed of polygonal or oval cells which contain dark, round, eccentrically situated nuclei and a delicate foamlike cytoplasm with small pigment granules.

roditism embryonic tumors are not uncommon. Such cases were described by Scully<sup>8</sup> in 1953, Ber<sup>1</sup> in 1949, Plate<sup>6</sup> in 1953, and Santesson and Marrubini<sup>11</sup> in 1957. From the histological point of view, these tumors are composed of germ cells alone (dysgerminoma) or germ cells and sex-cord type cells (granulosa or Sertoli cells).<sup>2, 7, 10</sup> Finally, there are occasional tumors composed of 3 cell elements: (1) germ cells, (2) sex-cord cells, (3) male mesenchymal cells (interstitial cells of Leydig or theca-lutein cells). According to Scully's nomenclature, these are classified as gonadoblastomas.

In cases with embryonic tumors and clinical and laboratory symptoms of androgen and estrogen activity, there usually are well-developed mesenchymal cells (Leydig or theca-lutein cells) or female sex-cord cells (granulosa or Sertoli cells) which produce appropriate hormones. As Scully<sup>8, 9</sup> correctly suggests, some of the embryonic tumors in the world literature that have been classified as dysgerminomas undoubtedly represent gonadoblastomas, especially

those which manifest androgen or estrogen activity.

An accurate histological study of specimens taken from these tumors is likely to lead to the discovery of female sex-cord type cells and the mesenchymal (interstitial) cells, besides dysgerminoma cells.

Adenoma of the hilus cells in a case of gonadal dysgenesis was first described by Stange,<sup>12</sup> who pointed out that hilus cells become exuberant under the influence of excessive secretion of gonadotropic hormones. Therefore, the question arises as to why, in cases of gonadal dysgenesis or male pseudohermaphroditism, embryonic tumors are so commonly found. It should be noted that among the 4 cases which have been described, 3 were genetically male. One may presume that in some cases of gonadal dysgenesis germ cells might have penetrated into the primary sex ridge zone at an early stage of embryonic life but were unable to find the necessary conditions for normal development in the malformed gonad. In the abnormal conditions of misshaped gonads, the development of cellular elements such as germ cells and sex-cord or interstitial cells may easily take the form of a tumor. Clinical experience seems to confirm this hypothesis.

### Summary

1. The authors present 13 cases of gonadal dysgenesis in which exploratory laparotomy was performed.

2. Histological examination of the gonads revealed one gonadoblastoma, two dysgerminomas, and one hilus cell adenoma. In all these cases tumors were found on only one side while on the other there were rudimentary gonads.

I would like to express my thanks to Dr. Robert E. Scully of the Massachusetts General Hospital, Boston, and to Professor Dr. K. Dux of Warsaw for their advice in the diagnosis of these gonadal tumors.

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# Junction of cancerous epithelium and stroma in the uterine cervix: electron microscope studies

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IN THE several studies of the normal cervical epithelium there has been shown to exist a definite submicroscopic structure representing a basement membrane.<sup>4, 5</sup> This thin membrane is beneath the stratified squamous as well as the columnar epithelium and surrounds the smaller vascular spaces. It is an easily identifiable line which appears to be almost literally intact across the entire area of junction.

The present study is an effort to determine the type of structure, if any, present at the coinciding area of carcinomatous epithelium and connective tissue of the cervical stroma.

## Method of study

Small pieces of tissue were removed from patients having proved squamous cell carcinoma of the cervix; these were cut longitudinally and fixed, one part in osmium tetroxide and the other in Zenker's fluid. The osmium-fixed tissue was thin-sectioned in methacrylate for examination by electron microscopy while the Zenker-fixed specimen was prepared in paraffin and stained with hematoxylin and eosin for light microscope.

## Observations

Fig. 1 shows the carcinoma-stroma junction where there is an electron dense line

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seemingly identical with the basement membrane seen under normal epithelium. The junction appears as a double line with a less dense zone between two dark stripes. As in the normal tissue, this double line appears to be made up of the membrane of the cell adjacent and a connective tissue component beneath, in close and constant apposition. The width of the double-layered structure is 350 Å. It is not possible to tell whether the membrane is made up of minute filaments, though none was observed under the highest magnifications which could be used with present tissue techniques.

Fig. 2 depicts a slightly different type of junction. There is a membrane visible but its integrity is not as perfect here as elsewhere in this and other specimens.

In Fig. 3 the carcinoma cell and connective tissue seem to join most casually without a visible membrane. The wall of the epithelial cell can be traced at the boundary but no basement membrane courses with it. However, the cell wall is sharp and clear at this region and at the line of contact with other cancer cells.

Another type of relationship exists at the junction illustrated in Fig. 4. There is a large pseudopod projecting from the cancer cell into the stroma. The remainder of the border is indistinct; neither cell wall nor basement membrane is clear.

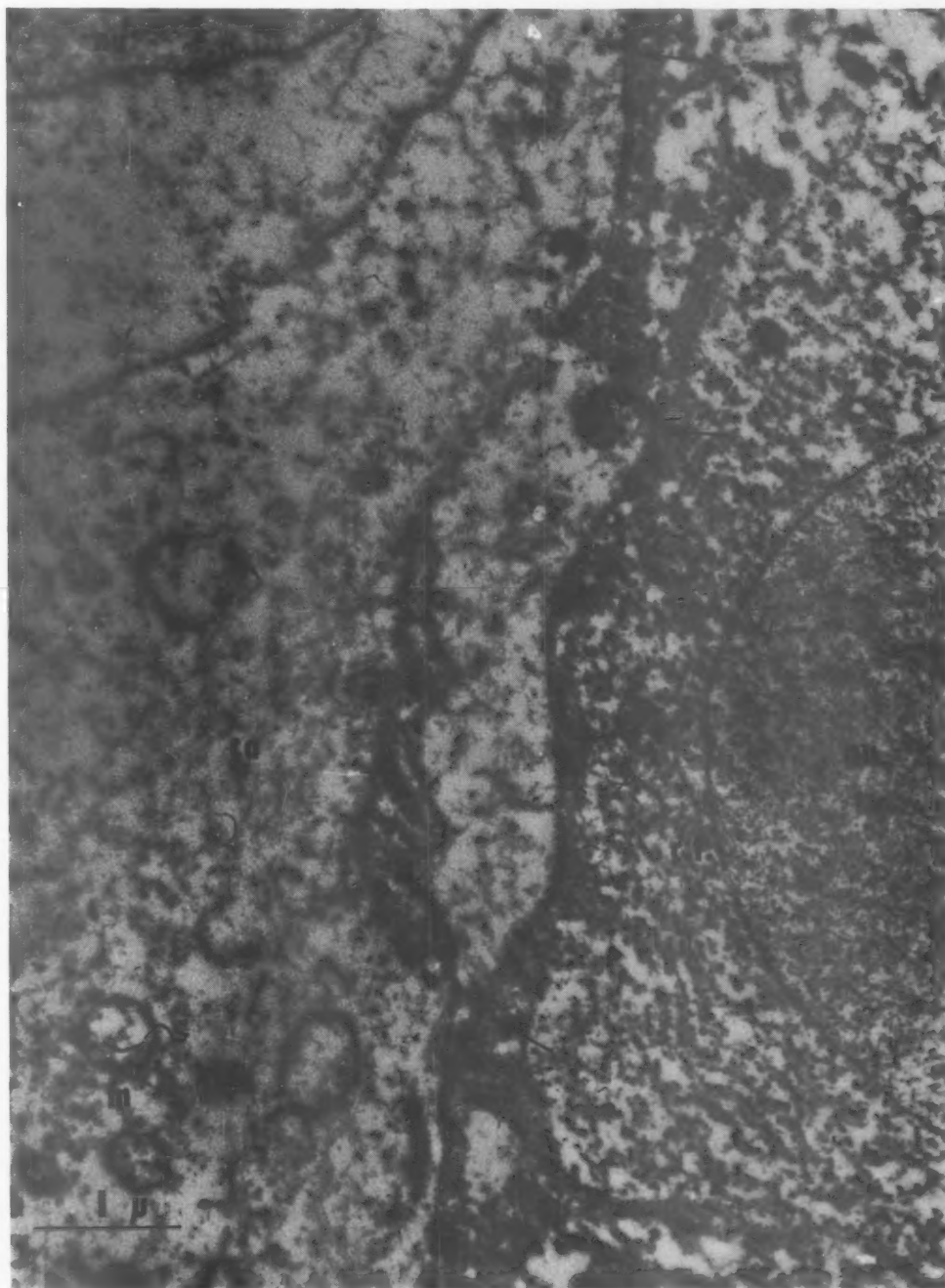
Still another morphological detail can be seen in Fig. 5. The epithelial cells joining the connective tissue exhibit lacelike villi along the boundary. These same projections form elaborate intertwining junctures with



other epithelial cells in regions where normally are found intercellular bridges. In this particular area there is no semblance of basement membrane.

#### Comment

Since there is so constant a structure beneath the epithelium in all preparations of normal cervix in the position occupied by



**Fig. 1.** Arrows indicate junction of carcinoma cells (*ca*) and connective tissue (*c.t.*) exhibiting an intact basement membrane. Width of membrane exclusive of cell wall is about 350 Å. Connective tissue cell nucleus, *nu*; mitochondria, *m*. ( $\times 28,500$ ; reduced  $\frac{1}{3}$ .) (One micron mark appears on this and all other micrographs.)

basement membrane, certain contrasts may be made in the instance of carcinoma of this organ. The details of composition of this junction are not as constant in the diseased state as in the normal, a fact necessitating explanation. The following points must be

taken into consideration in interpreting the micrographs.

**Artifact.** When thin sections of osmium-fixed tissues were first used, many of the details were considered to be produced by the processing.<sup>1</sup> With greater verification

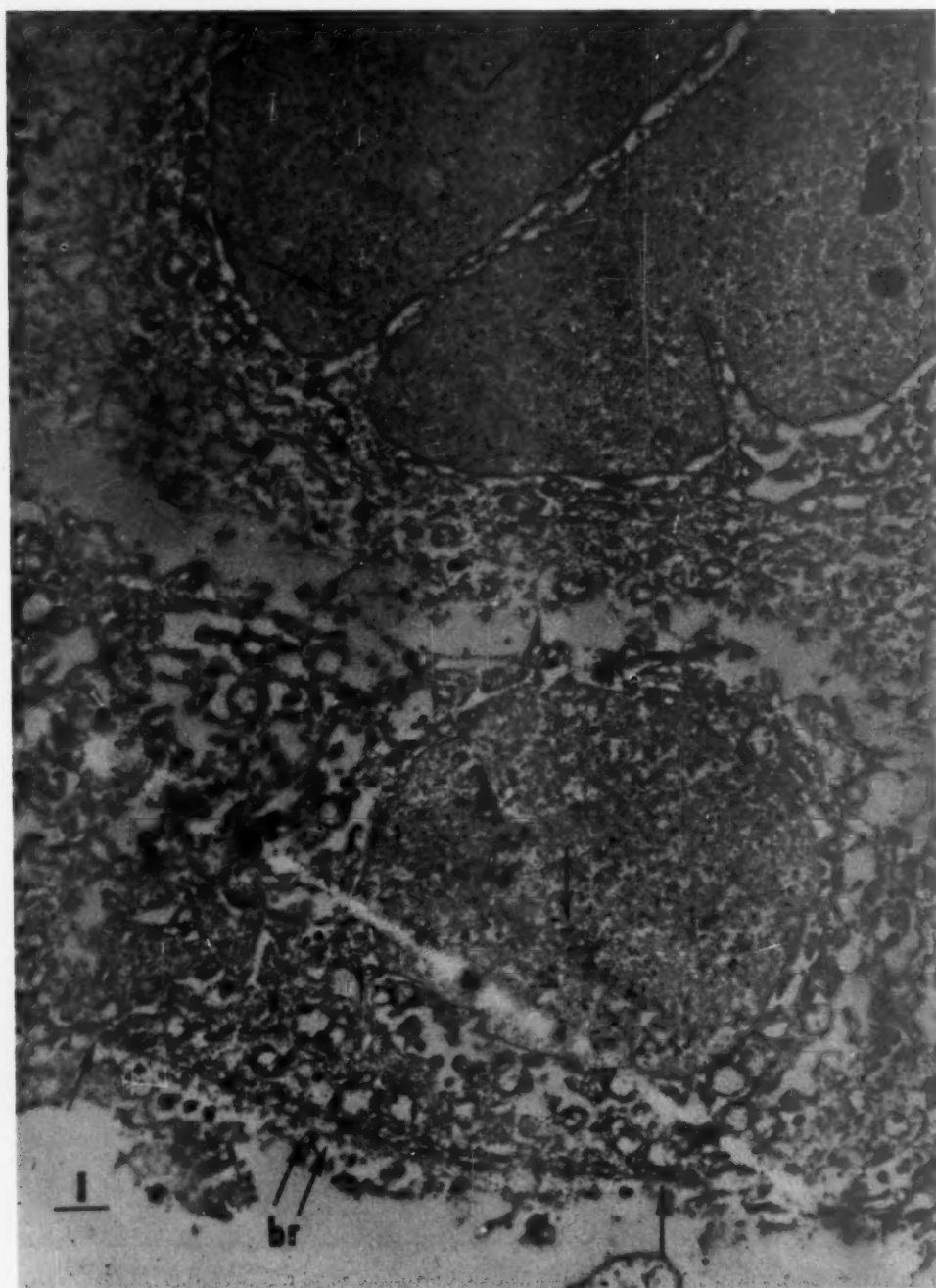


Fig. 2. Basement membrane with breaks (*br*) at several points. Two carcinoma cell nuclei are visible with condensation of chromatin indicated by arrows. ( $\times 10,500$ ; reduced  $\frac{1}{3}$ .)

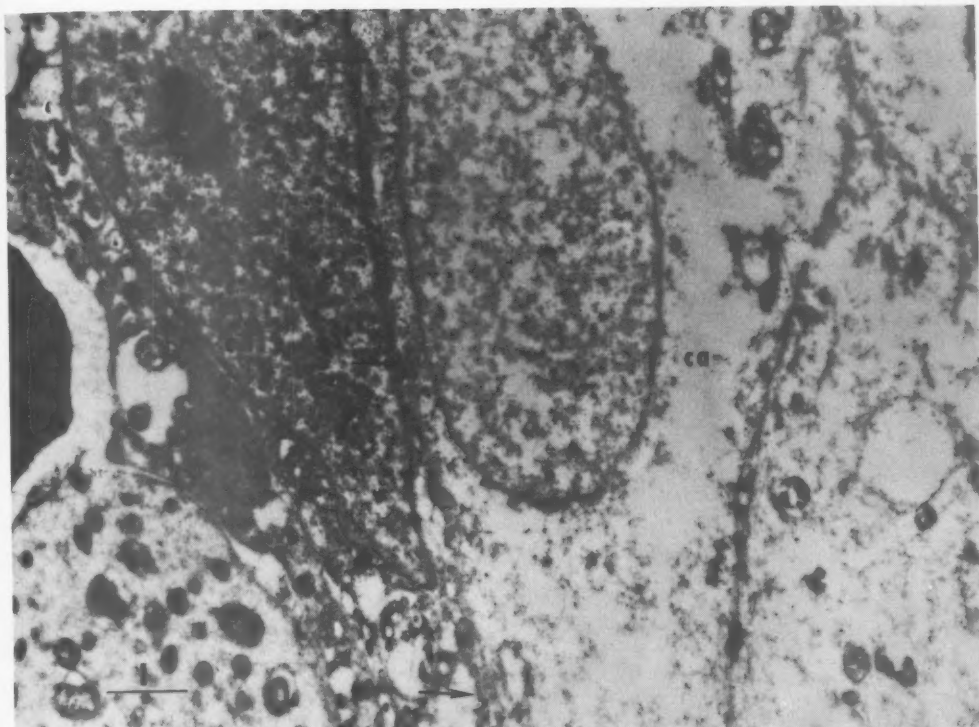


Fig. 3. Boundary of carcinomatous tissue indicated by arrows is made up of cell membranes of cancer cell (*ca*) and connective tissue cell (*c.t.*). ( $\times 20,700$ ; reduced  $\frac{1}{2}$ .)

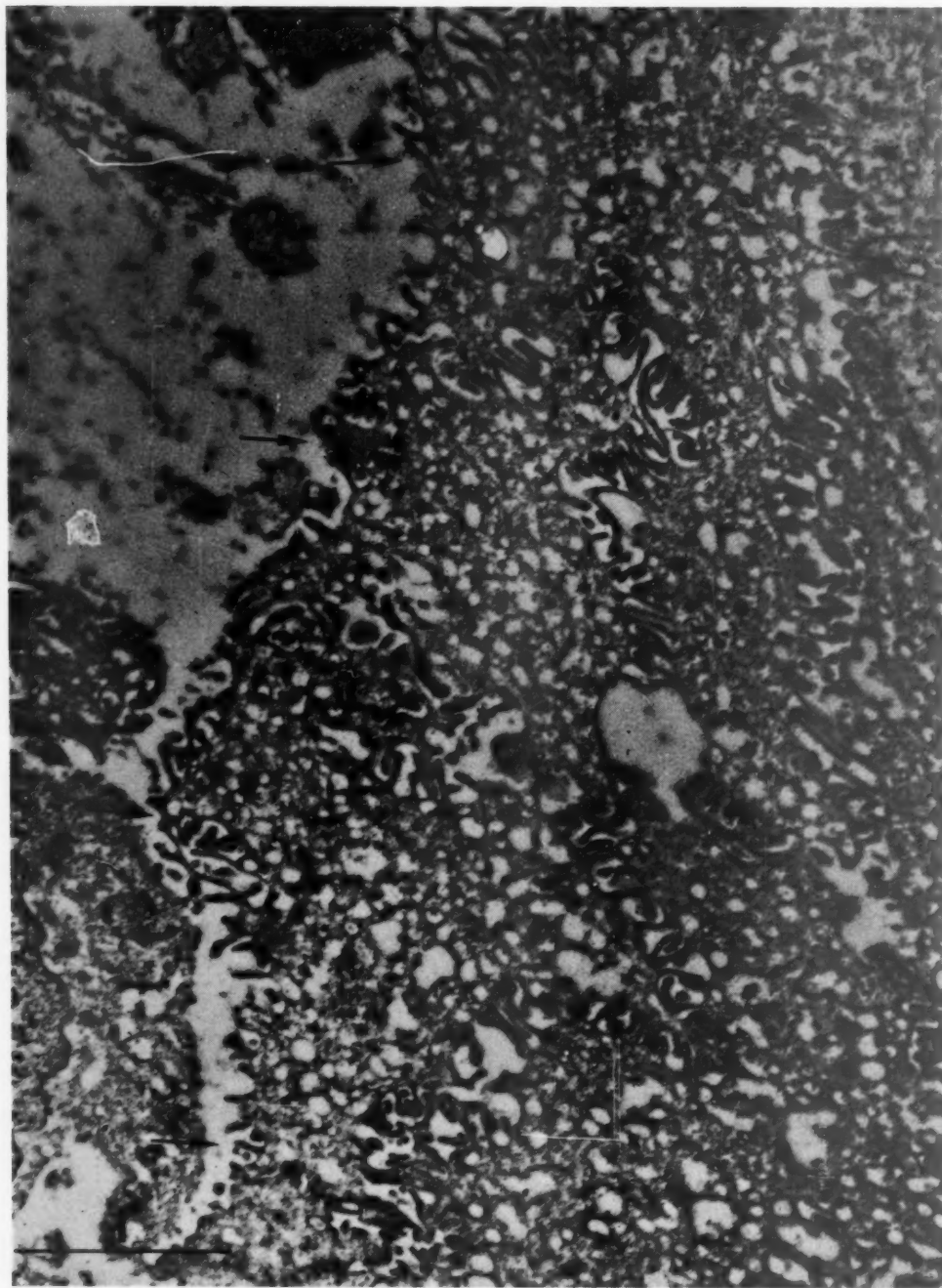


Fig. 4. Cancer cell exhibiting a large pseudopod (*ps*) protruding into the stroma. The membrane at this point appears indistinct. ( $\times 20,700$ ; reduced  $\frac{1}{2}$ .)

by more workers it became evident that structure at magnifications of the electron microscope was as constant and reliable as that seen at light microscope magnifications. It is no longer tenable to ascribe unusual or unsuspected ultrastructural details as due

to artifact. This would be particularly true of so definite a feature as basement membrane.

**Orientation.** A second obstacle to the study of thin sections is the difficulty in determining the direction and orientation of



**Fig. 5.** Arrows mark boundary of cancer cells and stroma. These cells all show complicated microvilli along the periphery, a feature thought to be associated with viral development. ( $\times 42,300$ ; reduced  $\frac{1}{3}$ .)



the section. It is comparatively easy to obtain a perpendicular section through normal epithelium showing, successively, superficial cells, intermediate cells, basal cells, junction, and connective tissue stroma. It is harder by far to obtain the same order in cancer tissue. There is evidence to indicate that the ultrastructure of superficial or intermediate cells (Fig. 5) differs from basal cells (Fig. 1), as does the epithelium-stroma border. One explanation usually advanced for the lack of sharpness of this boundary as sometimes noted (Fig. 4) is that it is cut at an angle from perpendicular. However, it is not possible to say whether "fuzziness" may not be a quality of the advancing edge of cancer.

**Variability.** Within the same specimen there are different relationships between the carcinomatous epithelium and the stroma. When first observed it was thought that this finding was due to inconsistency of technique or preparation. But after repetition of the observations it was concluded that there probably are a number of different relationships, ranging from presence of an intact basement membrane to complete absence of one. This is not surprising when it is recalled that the ultrastructure of cancer cells and organelles within cancer cells exhibit this same variability.<sup>2, 3</sup> It might be judged to be a property of carcinoma tissue that it is made up of areas which appear indistinct and unclear as well as areas which show sharp borders. The basement membrane seen in Fig. 1 is no less clear than that in normal cervical epithelium.

Two additional features observed in these cancer cells suggest, at least, the possibility of viral development within the cells. In

Fig. 2 arrows indicate dense aggregations of granular material within the nuclei. Morgan and associates<sup>6</sup> believe a similar stage can be identified in virus development in HeLa cells infected with certain respiratory type viruses, a stage just preceding the formation of intranuclear crystalline bodies.

In Fig. 5 fine cytoplasmic projections of the cell membrane make up a complicated microvillus pattern. This pattern has been observed in cancer cells by others.<sup>1, 5</sup> It has been suggested that viruslike particles are transferred from intracellular to extracellular positions through the microvillus system.<sup>1</sup>

### Conclusion

1. There is wide variation in structure at the junction of squamous cell carcinoma and cervical stroma. This border is marked by a well-defined basement membrane in some areas, by an indistinct membrane in others, and by no visible membrane at all in still other areas.

2. In certain areas of junction the structure is indistinct and "fuzzy." It is possible that this represents an advancing edge of the cancer.

3. Two features were observed in the sections of cancer cells which suggest a stage in virus development. Condensations of dense granular material within nuclei have been observed to precede the formation of intranuclear crystalline virus bodies. The microvillus pattern of the cell membrane is thought to be associated with transformation of intracytoplasmic viruslike particles to extracellular particles.

I wish to thank Dr. Frank Low, Director of the Electron Microscope Laboratory, for helpful criticism of all work during this study.

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# A histochemical study by fluorescence technique of the epithelial tumors of the cervix and uterus

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THE difficulties in distinguishing malignancies from normal, hyperplastic, and reactive conditions are commonly resolved by histological scrutiny of biopsy material. In some cases in which the clinical diagnosis is complicated, however, problems also arise in the elucidation of microscopic appearances. Hence, a continuous search has been and is being made for some means of separating malignant from innocent states.

This is of special importance in cases where only small amounts of material are available for study and in certain hyperplastic conditions where some degree of atypical cell growth has occurred. It applies also to states where localized changes of doubtful significance, mimicking neoplasms, are found. Such are carcinoma *in situ* and related conditions.

Since it has become apparent that morphological distinctions between neoplastic and nonneoplastic tissues may not be gross, attempts have been made to demonstrate staining differences between these cells; but such attempts have been unsuccessful, and the differences, as indicated by subsequent behavior, are of a more subtle nature than has been envisaged previously. Opportunities for study of this aspect of the problem have been made possible by the discovery of the chemical carcinogens and their application to experimental animals.

Increasing attention, therefore, is being directed to the physicochemical difference

between tumor cells and the cells of the tissue in which they arise. Interest was first evinced in this by the recognition of a specific binding of chemical carcinogens to certain cytoplasmic proteins of a susceptible organ or tissue. This binding was observed first in livers of rats fed 4-dimethyl-aminoazobenzene<sup>19</sup> and subsequently in the cells of the epidermis of mice following the local application of 3:4-benzpyrene and 1:2:5:6-dibenzanthracene.<sup>5, 6</sup>

These observations were given further point by the discovery that the carcinogen was not present in the tumor cells when a neoplasm developed. It was also shown that the particular cellular component involved was a protein or protein complex within the cytoplasm and that the bound carcinogen could be recovered only on hydrolysis of the protein. Its absence from the cytoplasm of tumor cells was demonstrated electrophoretically.<sup>3, 11, 20</sup>

These findings led to a number of hypotheses incorporating protein deletion as of causal significance in the mechanism of carcinogenesis. Green<sup>4</sup> postulated that the production of autoantibodies to the protein-carcinogen complex was an essential feature in the mechanism of protein deletion, and he cited the work of Weiler<sup>21-23</sup> in support of his concept. Weiler demonstrated the absence of certain proteins in the cells of rat hepatoma<sup>22</sup> and in experimentally induced renal tumors of the hamster<sup>24</sup> by using "organ specific" fluorescent antibodies. He attributed these observations to

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the loss of the "organ specific" antigens.

Examination of this phenomenon confirmed Weiler's observation but identical results were obtained by use of any globulins, even globulins from uninjected rabbits.<sup>7, 8</sup>

In order to determine whether this diminished affinity for fluorescein-globulin complexes was a peculiarity of rat hepatoma or whether it was a feature common to other neoplastic states, a systematic investigation into the staining characteristics of the different groups of tumors was carried out. Differential staining was observed between tumor cells on the one hand and normal and hyperplastic cells in a series of carcinomas of the colon,<sup>13</sup> epidermis,<sup>15</sup> and breast<sup>16</sup> and leukemias occurring in man<sup>14</sup> and in animals.<sup>17</sup> This has been demonstrated with the  $\gamma$  globulins of 13 different species of animals<sup>9</sup> as well as with the  $\alpha$  globulins and albumins of all these animals.<sup>10</sup> A similar staining result is being obtained with use of egg albumen.

Thus, the body of evidence discards any serological significance and indicates some nonspecific physicochemical reaction as being responsible for the differential staining.

Because of the importance of being able to demonstrate by histochemical means any difference between the malignant cell and its normal and hyperplastic counterpart, this staining reaction has been applied to a series of carcinomas of the cervix and uterus and the results of this investigation are presented here.

#### Methods and materials

**Preparation of sera.** Rabbit globulin fractions were prepared by precipitation with 50 per cent saturated ammonium sulfate at 1° C. and subsequent dialysis against phosphate-buffered saline pH 7.2. These were conjugated with fluorescein isocyanate by the method of Coons and Kaplan,<sup>2</sup> placed in 5 ml. sealed ampules, and stored in the dark in a freezing unit (-20° C.).

**Treatment of biopsy material.** All tissues examined were obtained from uterine curettage and cervical biopsy. In each case a small piece of tissue approximately 4 mm.

thick was selected and snap-frozen in pre-cooled isopentane (-70° C.) kept in a test tube which was immersed in an ethanol-dry ice mixture.

**Preparation of tissue sections.** Unfixed frozen sections were cut with a rotary microtome placed in a commercial freezing unit<sup>12</sup> and maintained at -20° C. The slides were placed in a wooden rack at an angle of 60 degrees from the horizontal position and dried in a cold room at 0-2° C. with the help of a fan for 1 to 2 hours, again immersed in cold ethanol for 15 minutes, and dried in the cold room overnight.

**Method of staining.** Prior to staining, the unbound fluorescein and its derivatives were extracted with ethyl acetate. This was done by adjusting the pH of the conjugate to 7.0 (bromothymol blue) with the addition of N. hydrochloric acid and then extracting the solution twice with 2 volumes of ethyl acetate. The supernatants were discarded and the dissolved acetate was removed from the aqueous phase *in vacuo* with a water pump.

The dried tissue sections were stained at room temperature. One or more drops of the conjugate, sufficient to cover the section, were placed on the slide and evaporation prevented by covering with a Petri dish. After 10 minutes, the conjugate was

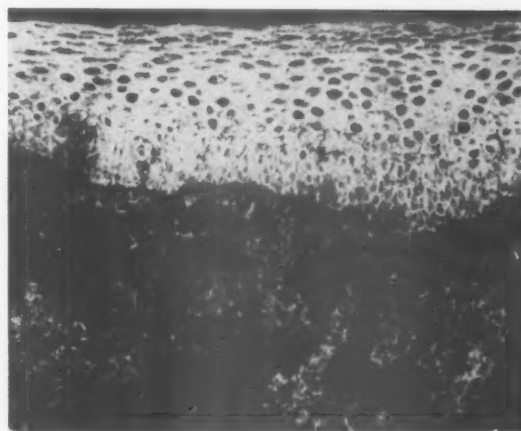


Fig. 1. Normal cervix. Fluorescence photomicrograph after staining with fluorescein-protein complex, showing a bright fluorescence of the cytoplasm of the epithelial cells. The nuclei do not stain. ( $\times 200$ ; reduced  $\frac{1}{4}$ .)

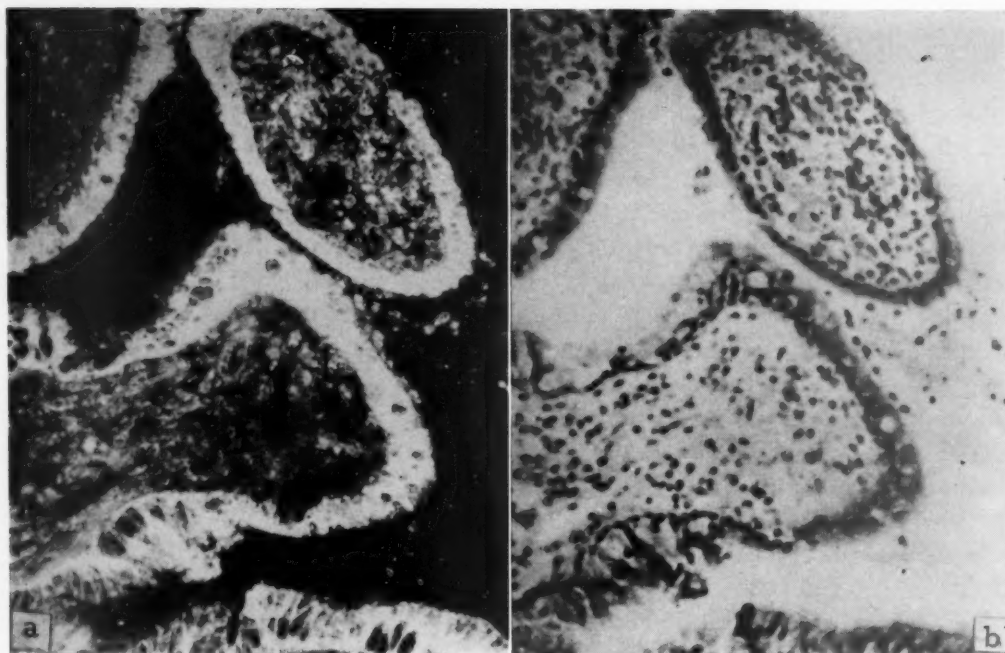


Fig. 2. Endocervix. *a*, Unfixed frozen section stained with fluorescein-protein complex and showing bright fluorescence of the tall columnar epithelium. *b*, Same area subsequently fixed in Formalin and stained with hematoxylin and eosin for comparison with *a*. ( $\times 240$ .)

decanted off and the sections washed in 3 changes of buffered saline, pH 7.3, for a further 10 minutes. The bottoms of the slides were quickly dried with a clean cloth and examined immediately with the fluorescence microscope without the use of any cover glass.

**Fluorescence microscopy and photography.** The source of light for ultraviolet microscopy was a 10 ampere D.C. carbon arc lamp with a clockwork feed (Leitz). Two BG 12, 4 mm. filters were placed between the light source and the condenser and a Wratten G 15 gelatin filter in the ocular.

A 35 mm. reflex type camera was employed and this was loaded with medium speed, fine emulsion film (Pan F). The exposure times varied from 75 to 90 seconds, depending on the intensity of the fluorescence.

After being photographed in ultraviolet light the sections were fixed in 10 per cent formol saline, stained with hematoxylin and eosin, and, for comparison, the same area

was again photographed by normal routine methods with visible light.

### Results

The staining characteristics of the epithelial tissues of the cervix and uterus were investigated by ultraviolet microscopy. The different types of tissues examined are shown in Table I. Sections from all these tissues were examined both in their natural state and after staining with fluorescein-globulin complexes in order to exclude the presence of any autofluorescence.

**Cervical epithelium.** The general finding was that only the cytoplasm of the stratified squamous epithelium lining the portio vaginalis of the cervix (Fig. 1) and of the columnar epithelial cells of the endocervix (Figs. 2 and 3) showed an affinity for fluorescein-globulin complexes and emitted a uniform bright green fluorescence in ultraviolet light. The nucleus of these cells, any additional cytoplasmic inclusions, such as vacuoles, and the minimal amount of intercellular cement supporting these cells



lacked this affinity and appeared as shadows in the dark background. In addition, the connective tissue cells and their intercellular substance, although present in relatively large amounts, also failed to show a positive staining reaction.

**Normal endometrium.** Both the proliferative and the secretory phases of the endometrial mucosa showed similar staining characteristics in that the cytoplasm fluoresced brightly and uniformly but the nucleus and cytoplasmic vacuoles failed to do so (Figs. 4 and 5).

In addition to the glands, the stromal cells also showed a positive staining reaction (Figs. 4 and 5) in which the cytoplasm did but the nucleus did not stain.

**Endometrial hyperplasia.** Examples of hyperplasia of the endometrium in various stages even to the most pronounced degree in which the endometrium is enormously overgrown and polypoid were obtained at curettage. Histologically the glands showed gross variation in size ranging from small groups of epithelial cells to large cystic

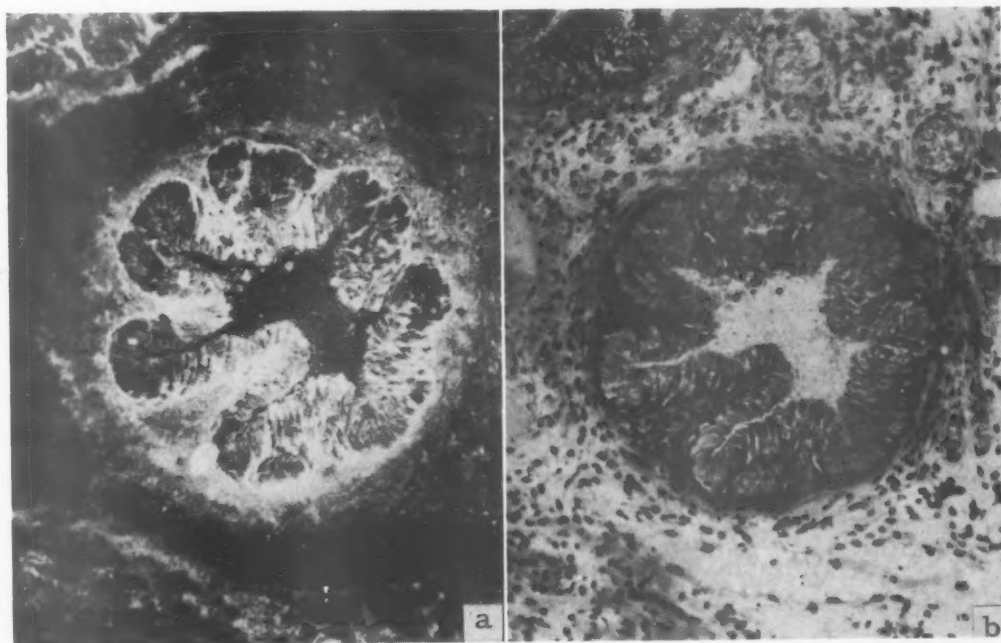
**Table I.** Results of fluorescence staining in the series of tissues examined.

<i>Tissue</i>	<i>No. examined</i>	<i>Fluorescence*</i>
Cervix (normal)	28	Present
Cervix (erosion)	11	Present
Endometrium (normal)	18	Present
Endometrial hyperplasia	9	Present
Endometriosis	4	Present
Cervix—epidermoid carcinoma	22	Absent
Cervix—adenocarcinoma	1	Absent
Uterus—adenocarcinoma (man)	2	Absent
Uterus—epidermoid carcinoma (rat)	1	Absent

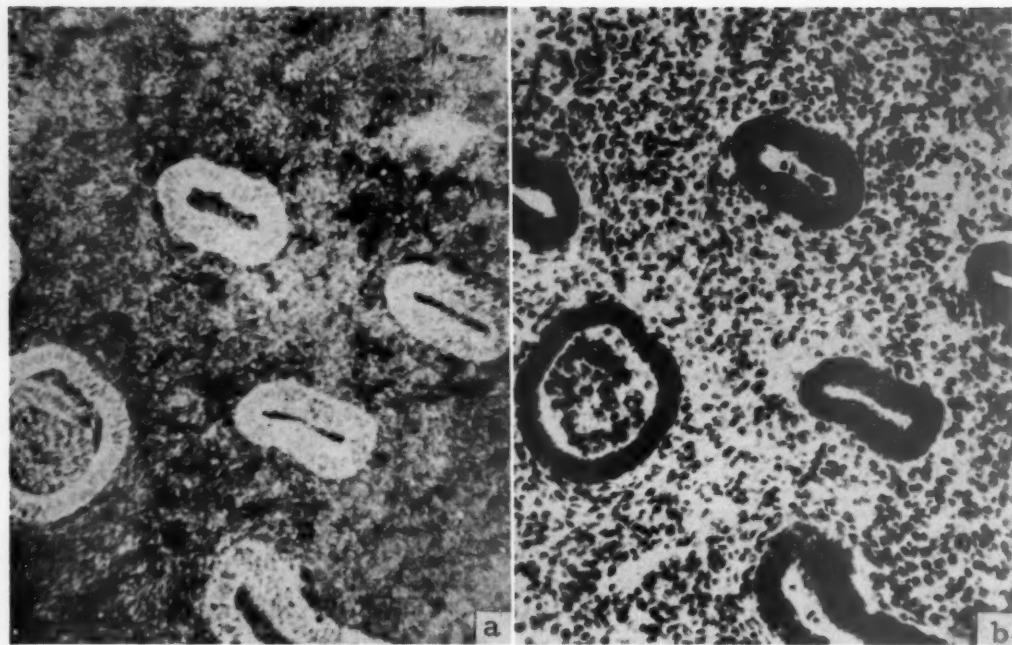
\*In all cases the normal and hyperplastic tissues stained brightly and uniformly but the malignant tissues failed to do so.

spaces. The cells lining the surface and glands were tall columnar with large nuclei and showed frequent mitoses. Similarly, the stromal cells were more closely packed and possessed an increased mitotic activity.

Both of the epithelial cells and stromal cells in these hyperplastic conditions fluoresced brightly and uniformly (Fig. 6).



**Fig. 3.** Cervical gland. *a*, Unfixed frozen section stained with fluorescein-protein complex and showing bright fluorescence of epithelial cells. *b*, Same area after fixation; stained with hematoxylin and eosin for comparison. ( $\times 240$ .)

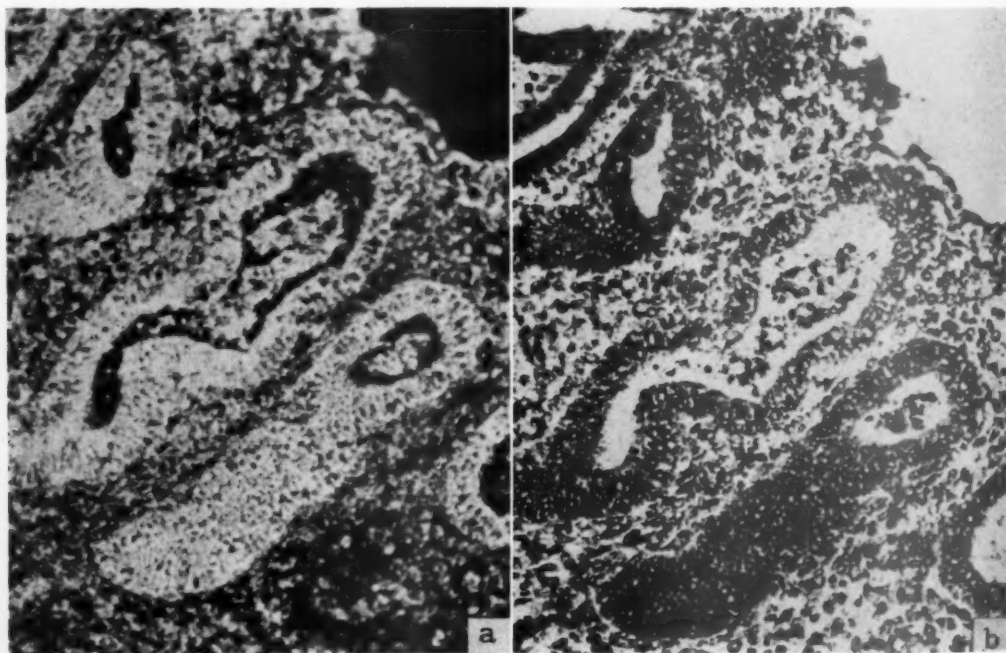


**Fig. 4.** Endometrium (proliferative phase). *a*, Unfixed frozen section stained with fluorescein-protein complex and showing the typical staining of glands. The stromal cells also stain. *b*, Same area subsequently fixed in Formalin and stained with hematoxylin and eosin for comparison with *a*. ( $\times 240$ .)

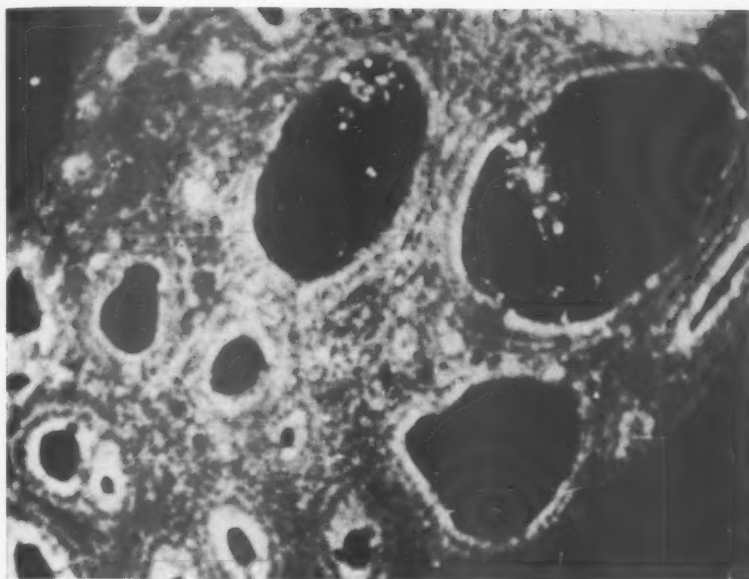
**Endometriosis.** Endometrial tissue composed of glands, epithelium, and stroma occurring deep to the uterine muscle fluo-

resced in the same manner as normal endometrium.

**Placental and fetal tissues.** These were



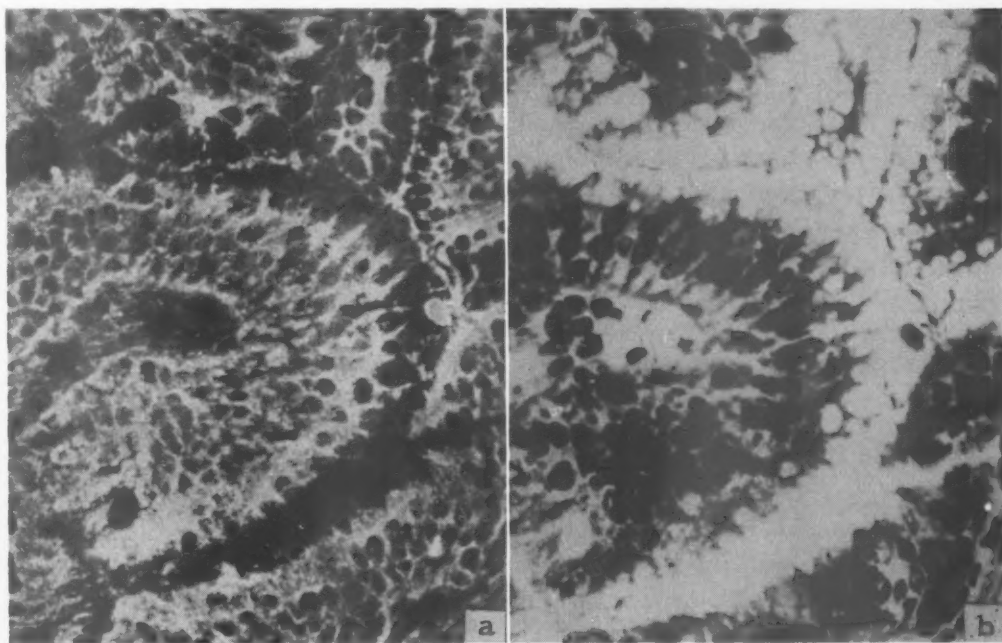
**Fig. 5.** Endometrium in secretory phase. *a*, Unfixed frozen section stained with fluorescein-protein complex, showing fluorescence of both glandular and stromal cells. *b*, Same area subsequently fixed in Formalin and stained with hematoxylin and eosin for comparison with *a*. ( $\times 240$ .)



**Fig. 6.** Cystic hyperplasia. Fluorescence photomicrograph of an unfixed frozen section stained with fluorescein-protein complex and showing bright fluorescence of both cystic and involuting glands as well as of stromal cells. ( $\times 240$ .)

obtained from the gynecological wards of the hospitals and from experimental animals. A good example of fetal tissue, that was always taken as the key tissue, was the

liver, but kidney, skin, and bowel were also examined. In all cases the cells stained in the characteristic fashion (Fig. 7). Another important tissue which could be examined at



**Fig. 7.** Bowel from a 14 day chick embryo. *a*, Fluorescence photomicrograph showing very bright fluorescence of the rapidly proliferating epithelium. *b*, Same area after fixation in Formalin; stained with hematoxylin and eosin for comparison with *a*. ( $\times 240$ .)



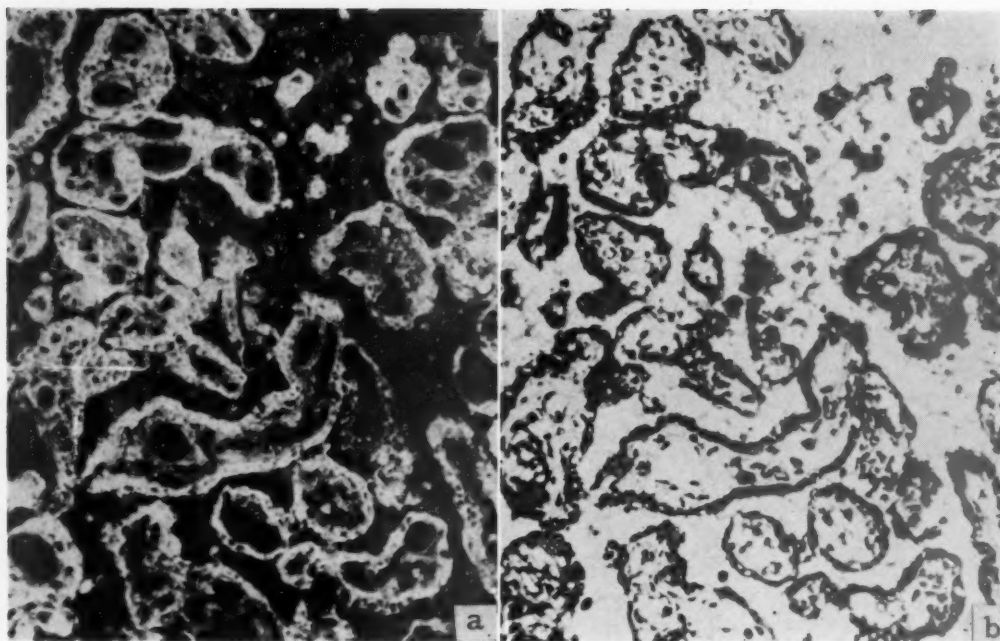


Fig. 8. Human placenta. *a*, Fluorescence photomicrograph showing bright fluorescence of all the cells lining the villi. *b*, Same area after fixation in Formalin; stained with hematoxylin and eosin for comparison with *a*. ( $\times 240$ .)

various stages was the placenta. This showed that both the Langhans and syncytial layer of the villi stained well and fluoresced brightly in ultraviolet light (Fig. 8).

**Neoplasms.** Finally, a number of tumors of the endometrium and cervix were investigated (Table I). The series included both the well-differentiated and undifferentiated types. In each case differential staining between normal and malignant tissue was demonstrated (Figs. 9, 10, and 11). Although in a large proportion of these cases only fragments of material obtained at curettage were examined, they were always sufficient to demonstrate whether or not the cells took up the stain.

#### Comment

The results described in this paper show that the sharp distinction between the cells of the carcinoma and those of the nonneoplastic counterpart which have been demonstrated in other groups of tumors<sup>13-17</sup> applies equally well to the tumors of the cervix and uterus.

In the series of 24 cases of carcinoma

which have been examined, the results were consistent in that there was a uniform failure of the neoplastic tissue to fluoresce after staining with fluorescein-globulin complexes. Such results were compared with those obtained after staining with a routine stain such as hematoxylin and eosin.

As a result of observations that have been carried out to date, the general finding has been that, in nonmalignant conditions, parenchymal cells stain whereas supporting tissues fail to do so. In some circumstances, however, groups of connective tissue cells also were noted to stain and to stand out clearly just as epithelial cells do. This problem has already been investigated and discussed<sup>18</sup> and the conclusion was reached that whether a cell stains or not depends on its volume of cytoplasm and its affinity for fluorescein-globulin complexes. This was found to be so, irrespective of whether or not the cell was of epithelial or of connective tissue origin.

In this regard, the staining of endometrial tissue was of particular interest. Both the glands and stroma stained in the normal



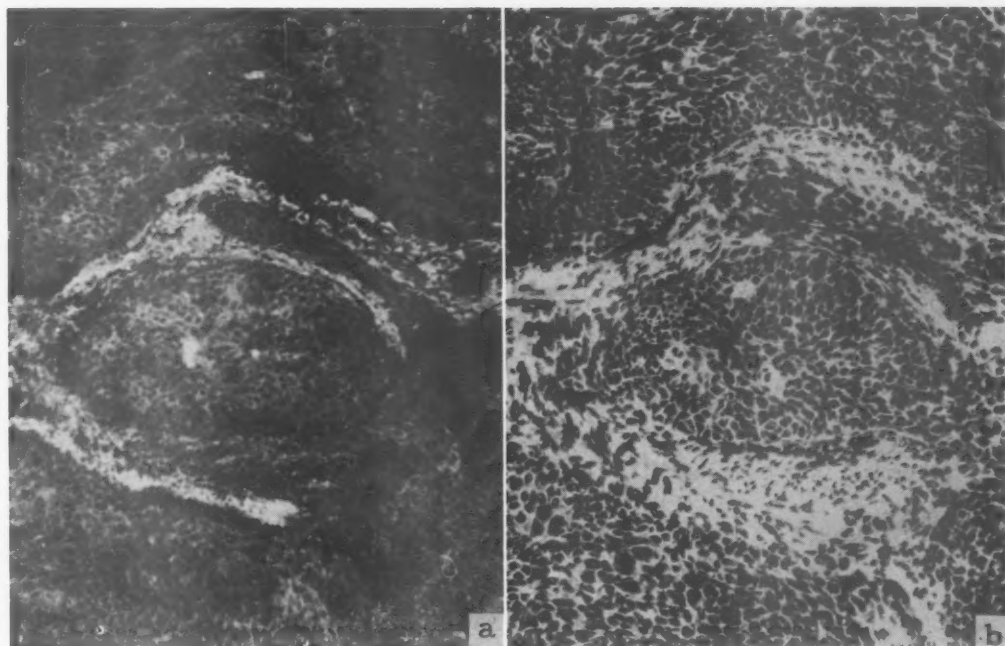


Fig. 9. Carcinoma of cervix. *a*, Fluorescence photomicrograph showing some linear autofluorescence (elastic tissue) and outlines of islands of cells. *b*, Same area after fixation in Formalin; stained with hematoxylin and eosin to show the structure of the nonfluorescing cells. ( $\times 200$ .)

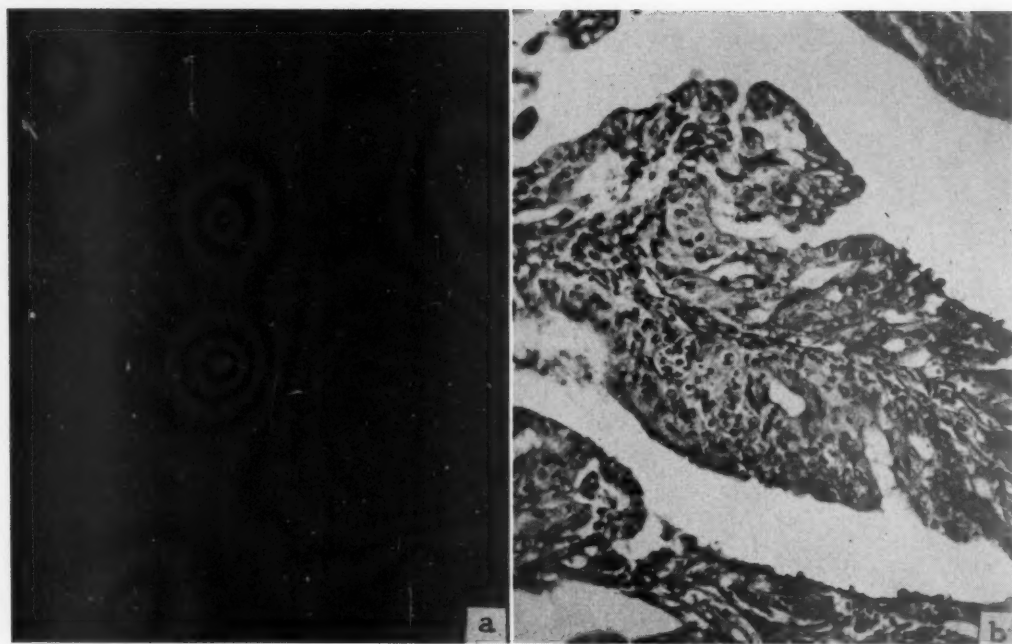
fashion, that is, the cell cytoplasm, but not the nucleus, stained and fluoresced in ultraviolet light (Figs. 4 and 5). It is incidentally interesting that stromal cells and gland epithelium are more closely related histogenetically than was previously thought.<sup>1</sup> However, this staining of the stromal cells simply means that the cells possess a sufficient amount of cytoplasm with an affinity for the dye to enable visualization. The question of the origin of the cells, therefore, need not be discussed since it is now clear that cells of different forms may show similar staining characteristics provided that they have sufficient cytoplasm.

Thus, examples of endometrium in all phases of the menstrual cycle showed a well-developed fluorescence of both epithelial and stromal cells. Such positive staining is of particular interest here because of the gross physiological and biochemical changes that take place within the cells. The increased thickness of the endometrium which occurs during the secretory phase is due partly to the cells of the glands and

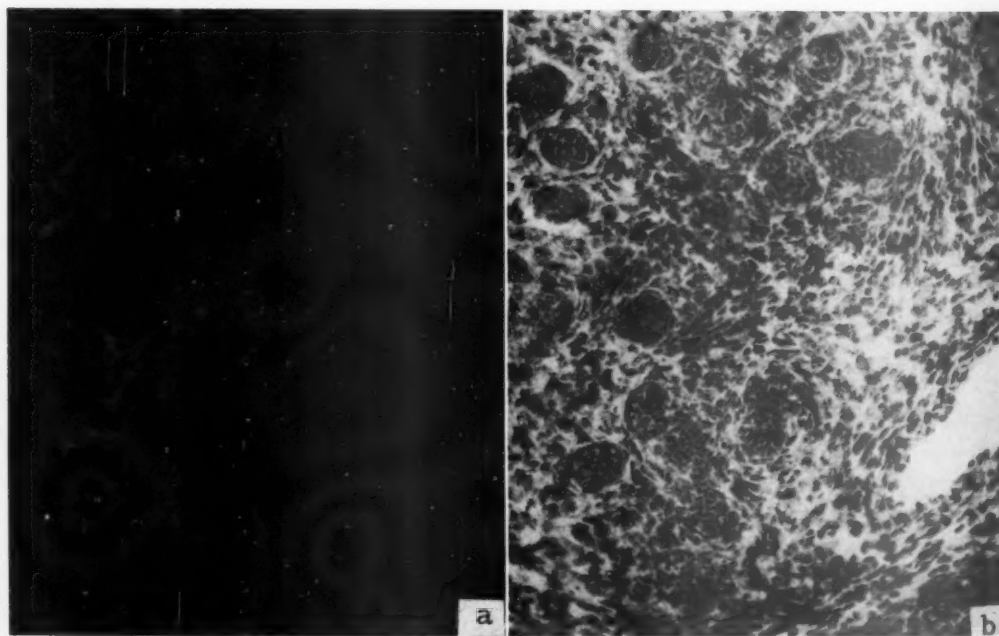
stroma dividing by mitosis and partly to the glands' accumulating increased amounts of secretion. Finally, in the latter stages, the cells come to contain considerable amounts of glycogen and other secretions. None of these factors affect in any way the affinity of the cytoplasm of the cells for the stain, though cytoplasmic inclusions like the nuclei do not stain.

The hyperplasias, especially those referred to as metropathia hemorrhagica, all fluoresced in the same manner as normal endometrium. Although the distinction from carcinoma is easy, it is, nevertheless, of interest to find that such gross polypoid conditions which show an increase in the number of both epithelial and stromal elements do stain like normal tissue.

In the case of endometriosis, the basal tips of the endometrial glands which appeared to burrow in the myometrium as well as the ectopic glands and stroma again stained in the same way as the overlying normal or hyperplastic mucosa. It has been recognized for decades that the invasive glands of endometrium are not neoplastic



**Fig. 10.** Carcinoma of body of uterus. *a*, Unfixed frozen section stained with fluorescein-protein complex. There is lack of fluorescence but the outline of the connective tissue can be seen. *b*, Same area subsequently fixed in Formalin and stained with hematoxylin and eosin to show the structure of the nonfluorescing tissue. ( $\times 200$ .)



**Fig. 11.** Carcinoma of uterus (rat). *a*, Unfixed frozen section stained with fluorescein-protein complex, showing only a weak linear background fluorescence of the connective tissue. *b*, Same area after fixation in Formalin; stained with hematoxylin and eosin and showing that the nests of squamous cells failed to fluoresce in *a*. ( $\times 200$ .)

in character and the staining features shown here conform with what would be expected from previous information.

The importance of the study of embryonic or actively growing normal tissue became apparent. There was the possible relationship between embryonic and malignant tissues and it was probable that there might have been other differences which had not been appreciated from the observation of ordinary adult tissues. The positive staining reaction of all these cells differentiates them sharply from their malignant counterparts.

All types of obvious neoplasms of the cervix and uterus in this series failed to stain. In the uterine groups of tumors, both the epithelium and stromal cells showed a diminished affinity for the conjugated dye and failed to fluoresce in ultraviolet light. The minute amounts of material obtained in these cases was not sufficient to have normal and neoplastic tissue in the same section, but it was always sufficient to enable adequate observations of the tumor tissues.

In the case of the cervical tumors, on the other hand, it has been possible to obtain biopsy specimens from the tumor as well as from the adjacent and histologically non-neoplastic area. Although the tumor tissue here uniformly failed to fluoresce, the

adjacent histologically innocent tissue did show patchy areas of lack of staining. Such areas were composed of small groups of squamous cells and are probably similar to those initially observed in the livers of rats fed 4-dimethyl-amino-azobenzene which were referred to as "islands of loss" because they constituted a "precancerous state," as was shown by the eventual development of frank tumors. Similar areas were seen in the skin,<sup>15</sup> polyps of the colon in a case of multiple polyposis,<sup>13</sup> and in the breast.<sup>16</sup>

The value of this method of study, therefore, is not only to differentiate between normal and neoplastic cells but also to distinguish between hyperplastic and preneoplastic tissues. In this case this would apply with special significance to carcinoma in situ of the cervix uteri. Thus, the application of the fluorescein-globulin as a stain of nonspecific character appears to be a most useful tool in the diagnosis of malignancy as well as in aiding further fundamental studies in cancer research.

I am very grateful to Dr. H. Bettinger, Director, Department of Pathology, Royal Women's Hospital, for supplying biopsy material and for his keen interest in this work.

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# Histochemical methods applied to benign and malignant squamous epithelium of the cervix uteri

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HISTOCHEMISTRY is used to localize the specific substances present in the different cell layers which compose the tissue. By comparing the histochemical characteristics in normal and cancerous tissue it is hoped to acquire knowledge about the chemical differences between these tissues of possible importance for diagnosis and therapy.

## Material

Cervical material was obtained by punch and cone biopsy of 37 proved cases of cancer in situ and invasive cancer. In each instance normal cervical epithelium was studied as a control. Some studies were performed with squamous cancer of the esophagus and tongue as well as breast cancer; these are not included in this study.

## Methods

For nonenzymatic reactions dry mounted paraffin sections were used. For enzymatic reactions frozen sections were cut. Of 37 proved cases of cancer in situ and invasive cancer, 10 were examined by paraffin sections and 27 by frozen sections. Fifteen to 20 microsections were made from each case

so that more than 500 microsections offered about 40 examples of 12 staining techniques. Some of the material used for examination of enzymes was fixed for 2 to 4 hours in cold 10 per cent formalin (pH 6.5) at 4° C. and some, such as dehydrogenase, in acetone at 4° C. That fixative was used which would cause least destruction of the enzyme. Frozen sections were cut 10 m $\mu$  thick and were mounted in glycerine jelly. Paraffin sections were mounted in Permount. Every section of malignant tissue was accompanied by a section of normal tissue treated similarly for comparison. A routine hematoxylin-eosin stain was made of every case to compare with the specific stains (Figs. 1 and 19). In nonenzymatic reactions we did not use counterstain except in the Best stain. Enzymatic reactions were stained with and without counterstain with hematoxylin for comparison except for the phosphamidase reaction which shows nuclear staining. With use of counterstains, the preparations looked better, but the reaction became complicated. Every reaction was accompanied by controls in which the substrate was omitted or the tissue heated to destroy the enzyme to prove the specificity of the reaction.

In proving the action of reagents to investigate chemicals there is always the difficulty of the varying reaction of the stains in different slides, depending on the time the stain is used, the pH, the individual treatment of the slides, etc. It has been noticed that even though the slides are from the same patient and taken at the same time,

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a difference in the stain take-up was shown. As much as possible, therefore, our method of choice was to have the benign and malignant epithelium together on one slide, even one microscopic field. In this way we are sure that both kinds of epithelia are treated and stained in the same way and different qualities are really pathognomonic for the tissue in question. The transforma-

tion of benign to malignant epithelium is seen as a line rising from the basal layer to the superficialis formed by the increasing number of proliferating basal cells.

Reactions were carried out for glycogen (Best reaction), polysaccharides (PAS reaction), desoxyribonucleic acid (DNA), and ribonucleic acid (RNA) combined, (methyl green-pyronin reaction), DNA (Feulgen

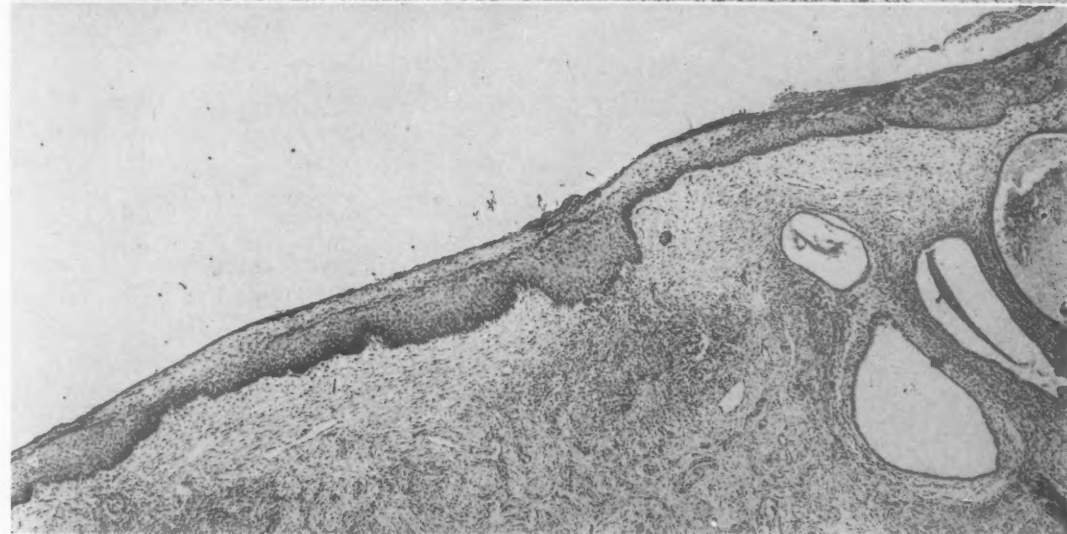
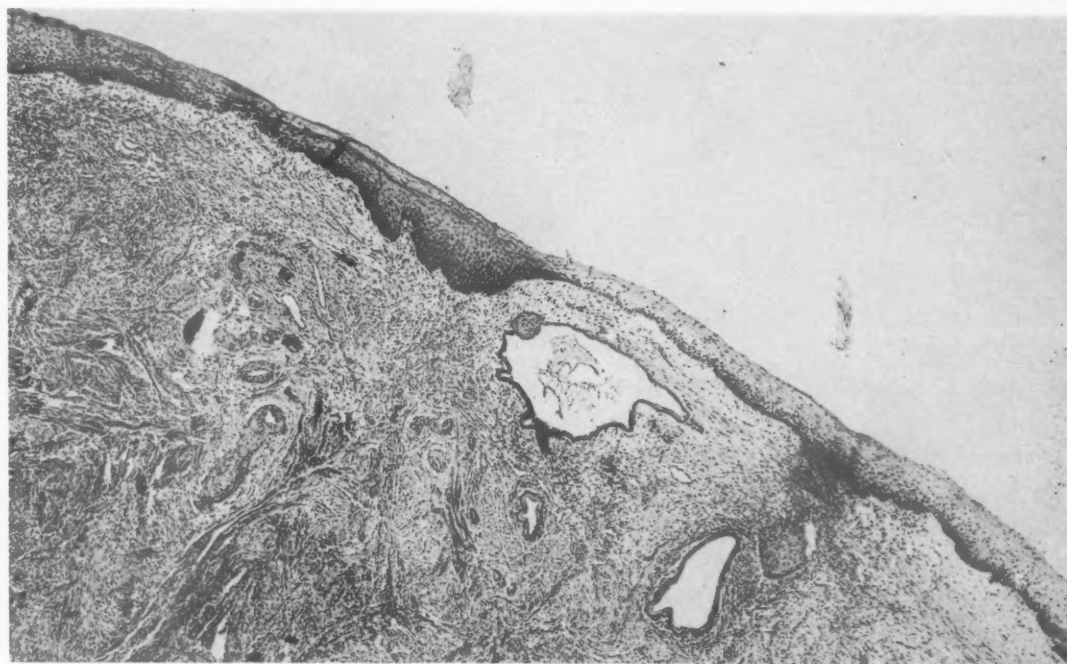


Fig. 1. Hematoxylin and eosin stain of slide showing normal epithelium to the right changing to basal cell hyperplasia and cancer in situ to the left. ( $\times 50$ ; reduced  $\frac{1}{6}$ .)

Fig. 2. In the normal tissue at right, no glycogen in the basal layer. Increasing amounts in the superficial layers. The superficial layers in the abnormal tissue to the left show decreasing quantities of glycogen. (Best and hematoxylin stain.  $\times 50$ ; reduced  $\frac{1}{6}$ .)

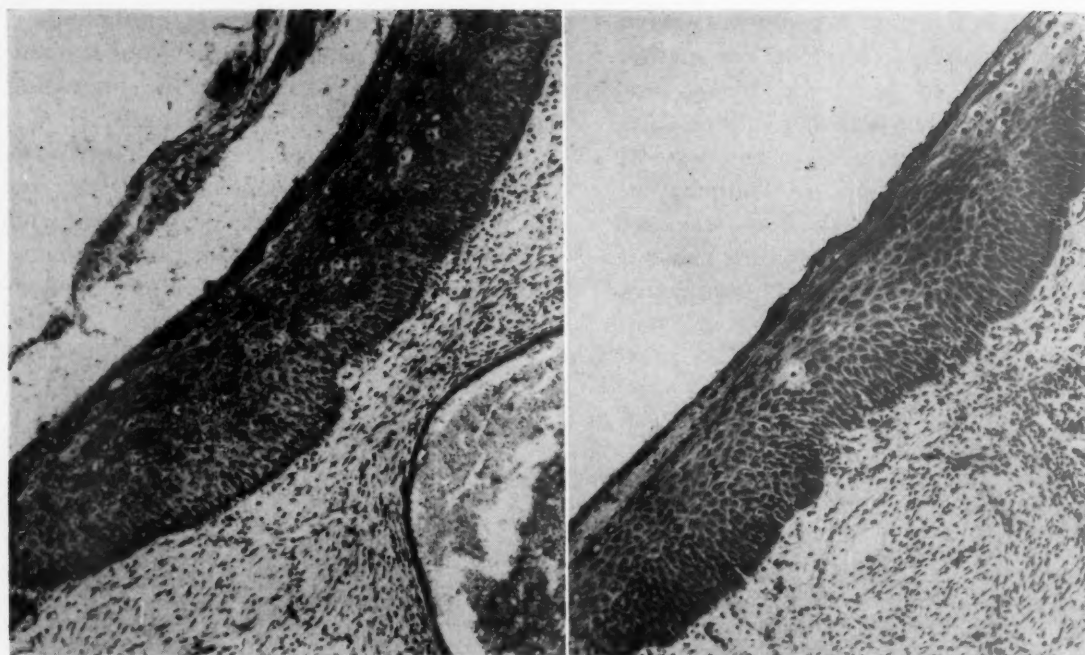


Fig. 2A. Magnification of Fig. 2. Normal part of the epithelium. Glycogen in the superficial layers. (Best and hematoxylin stain.  $\times 130$ ; reduced  $\frac{1}{3}$ .)

Fig. 2B. Magnification of Fig. 2. Abnormal part of the epithelium. Little or no glycogen in the superficial layers. (Best and hematoxylin stain.  $\times 130$ ; reduced  $\frac{1}{3}$ .)

reaction), the sulfhydryl reaction with Bennett's reagent, and the reactions of SS groups with methylene blue and cobalt sulfide. The enzymatic reactions studied were: acid and alkaline phosphatase, phosphamidase, esterase, glucuronidase, and dehydrogenase.

#### Specific procedures and results

**Glycogen (Best reaction).** In normal tissue, the basal layer has little or no glycogen. Going from the basal to the superficial epithelial layer the amount of glycogen increases. In the superficial layers, the Best reaction shows a distinct deep red stain. In cancerous tissue following the rising line of the surface of the basal layer we pass from the normal epithelium to the region of basal cell hyperplasia and to cancer in situ and find a decreasing amount of glycogen visible in the superficial layer, not only dependent upon the decreasing number of superficial cells, but also qualitatively in the superficial cells. The amount of glycogen corresponds well to the degree of differentia-

tion of the cells (Figs. 2, 2A, 2B, 3, and 4).

**The PAS reaction (McManus).** This showed that in normal tissue the basal layer has little or no polysaccharide. Passing to the superficial epithelial layer the PAS reaction increases. In cancerous tissue along the rising line of normal epithelium, basal cell hyperplasia and cancer in situ a decreasing amount of PAS material is visible in the superficialis, an amount corresponding well to the degree of differentiation (Figs. 5, 6, and 7).

**The methyl green-pyronin reaction (Pappenheim).** This was used to stain DNA of the nucleus and RNA of cytoplasm and nucleolus. Following the surface line of the basal cell layers toward basal cell hyperplasia and cancer in situ there occurred an increase of both stains. Cancer cells show a moderate increase in staining quality for DNA and a marked increase in their cytoplasm for RNA (Figs. 8, 9, and 10).

**The Feulgen staining method.** This method is based on the Schiff reaction for aldehydes. It is used to detect the presence

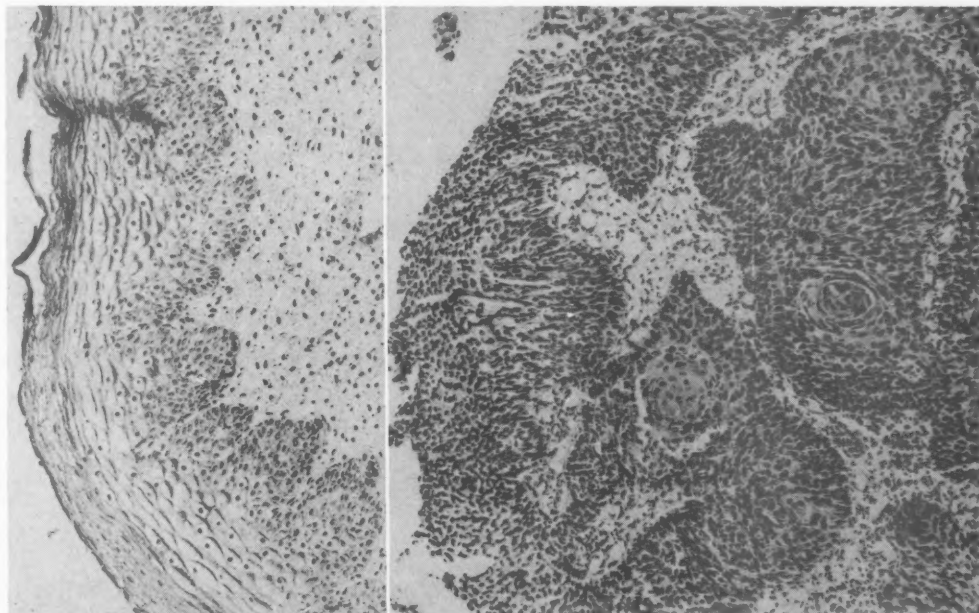
of DNA by acid hydrolysis of the nucleoproteins resulting in desoxyribose, an aldehyde, followed by application of the Schiff reaction. Although the resulting reaction was weak as a result of the high temperature to which the tissue was exposed during the hydrolysis, there was still a moderate though irregular increase of DNA detected in the staining intensity of cancer cell nuclei (Figs. 11 and 12).

**The sulfhydryl (SH) groups.** When present in animal tissue, these are bound to amino groups. The Bennett method is based on the reaction between mercaptans like chloromercuriphenylazo naphthol, a red dye, called sulfhydryl reagent (RSR) with SH groups. The reaction product is poorly soluble and diffusible, and it stains orange. In our tissue section, following the line from the normal to the cancerous tissue, the reaction was most intense in the basal layers, weaker in the superficial layers, and slightly stronger in the cancerous tissue (Figs. 13, 14, and 15).

**Disulfide (SS) groups.** Methods for disul-

fide (SS) groups are based on reduction methods by potassium cyanide or oxidation of cystine groups by performic acid and peracetic acid. In the case of SS, peracetic acid may be less efficient than performic acid as an oxidizing agent, but was preferred by us, performic acid being less stable, too difficult to handle, and too damaging to the tissue. The oxidized tissue was then stained with  $\frac{1}{2000}$  M methylene blue at pH 2.6 or treated with 2 per cent cobalt nitrate followed by diluted ammonium sulfide to give blue or black stainings, respectively. In our studies, superficial cells of cornified layers are strongly stained, as are some of the basal cell elements, being oxidized to cystine groups. The intermediate cell elements show very little stain. Cancer cell formations had a lower color intensity than the normal squamous cell formations (Figs. 16, 17, and 18). Pearl formation in cancerous tissues were strongly stained because of their large keratin content.

For enzymatic reactions formalin or acetone at 4° C. was used as tissue fixative be-



**Fig. 3.** Normal cervix. In the normal cervix, the epithelium is increasingly stained toward the superficial epithelium. (Best and hematoxylin stain.  $\times 160$ ; reduced  $\frac{1}{3}$ .)

**Fig. 4.** Cancer of the cervix. Nuclei of cancer cells stain stronger than the normal cell nuclei with hematoxylin, but cytoplasm does not take the carmine stain. (Best and hematoxylin stain.  $\times 150$ ; reduced  $\frac{1}{3}$ .)



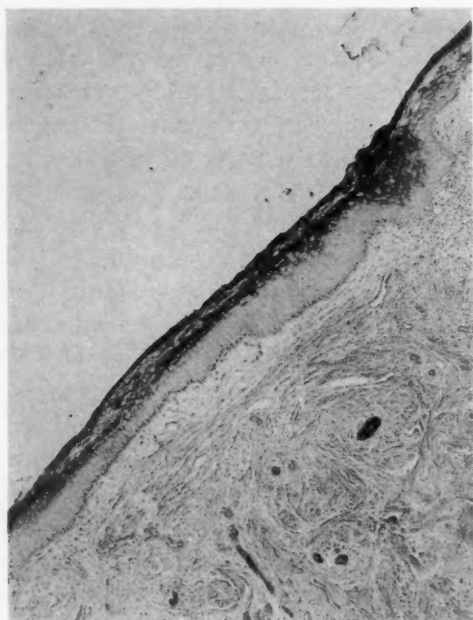


Fig. 5. PAS reaction. Strong reaction in the normal superficial epithelium (top). Decreased reaction in the abnormal epithelium (bottom). ( $\times 54$ ; reduced  $\frac{1}{3}$ .)

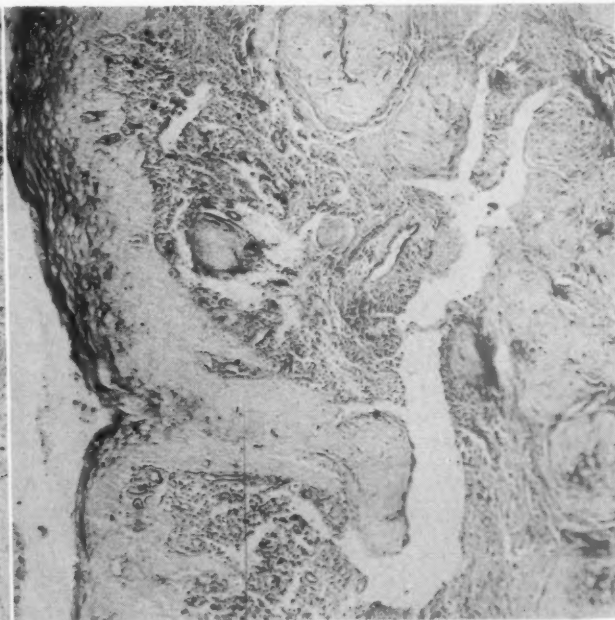
cause these fixatives have shown a different percentage of enzymatic activity remaining after fixation. This is particularly true for

succinic dehydrogenase which loses a great deal of its enzymatic activity after fixation in Formalin; fixed in acetone it maintains a strong activity. The period of fixation was 2 to 4 hours. For enzymatic reactions no embedding in paraffin was applied because much of the enzymatic activity was lost by this procedure.

**Dehydrogenase reactions.** For dehydrogenase reactions tissue was fixed in acetone and frozen sections were cut at  $10\text{ }\mu$ , mounted on slides, and stored at  $4^{\circ}\text{C}$ . in 0.1 per cent sodium cyanide. Sodium succinate was used as hydrogen donor, neotetrazolium chloride as substance to be reduced to diformazan (blue) or monoformazan (reddish) depending on the degree of reduction. The tissue showed a reddish reaction in the superficial epithelium increasing along the basal membrane to dark blue pigment formations. When normal was compared with cancerous tissue, there was a moderate quantitative increase of the reaction. Along the basal border of growing cells there was a strong reaction of dehydrogenase, but in cancerous tissue with many lay-



6



7

Fig. 6. PAS reaction. Normal cervix. In normal tissue, the PAS reaction increases from the basal to the superficial cells. Endocervical glands also show strong reaction. ( $\times 140$ ; reduced  $\frac{1}{3}$ .)

Fig. 7. The PAS reaction is not present in the cancerous tissue to the right and bottom of the picture. Some normal epithelium is present at the left top of the picture, showing some PAS-positive material. ( $\times 120$ ; reduced  $\frac{1}{3}$ .)



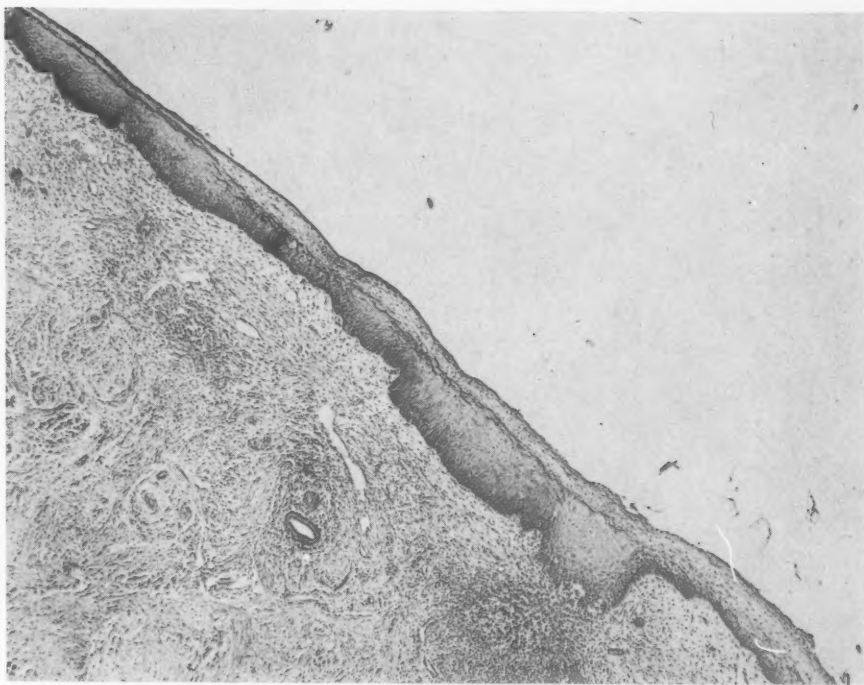


Fig. 8. Increase of the reaction in the cancerous epithelium to the left. (Methyl green-pyronin.  $\times 50$ ; reduced  $\frac{1}{2}$ .)

ers of cells there was a definite decrease of dehydrogenase reaction in the central layers. However, the reaction varied in different parts of the tissue (Figs. 19, 20, and 21).

**Alkaline phosphatase reaction.** For alkaline phosphatase reaction short fixation in cold Formalin ( $4^{\circ}\text{C}$ . for 2 to 4 hours) was performed, and frozen sections were cut. Sodium  $\alpha$ -naphthyl phosphate was used as substrate in veronal acetate buffer at pH 9.2. This was coupled to a diazonium salt (azo coupling technique of Pearse). We used 4-benzoylamino 2:5-dimethoxyaniline (diazo fast blue RR). A dark blue or black precipitate formed in locations of a positive reaction. Comparing normal with cancerous tissue there was a moderate quantitative increase of the reaction in cancerous epithelium (Figs. 22, 23, and 24).

**Acid phosphatase.** For acid phosphatase short fixation in cold Formalin ( $4^{\circ}\text{C}$ . for 2 to 4 hours) was performed and frozen sections were cut. Sodium  $\alpha$ -naphthyl phosphate was used as substrate in Michaelis buffer at pH 5. This was coupled to the

diazotate of o-dianisidine (fast blue B salt). A dark red or black precipitate occurred in locations of a positive reaction. Compared with normal tissue there was a marked quantitative increase of the reaction in cancerous epithelium (Figs. 25 and 26).

**Phosphamidase.** For phosphamidase short fixation in cold Formalin ( $4^{\circ}\text{C}$ . for 2 to 4 hours) was used and then frozen sections were cut. p-Chloranilidophosphonic acid served as substrate according to Gomori. A maleate buffer was employed and manganese ions used as an activator. The pH was at 5.6. With lead nitrate, the corresponding phosphate is treated with dilute ammonium sulfide resulting in lead sulfide as black precipitate in locations of positive reaction. Comparing with normal tissue a marked quantitative increase of the reaction in cancerous epithelium was found (Figs. 27 and 28).

**Esterase.** For the esterase reaction short fixation in cold Formalin ( $4^{\circ}\text{C}$ . for 2 to 4 hours) was performed and frozen sections were cut.  $\alpha$ -Naphthyl acetate in acetone at

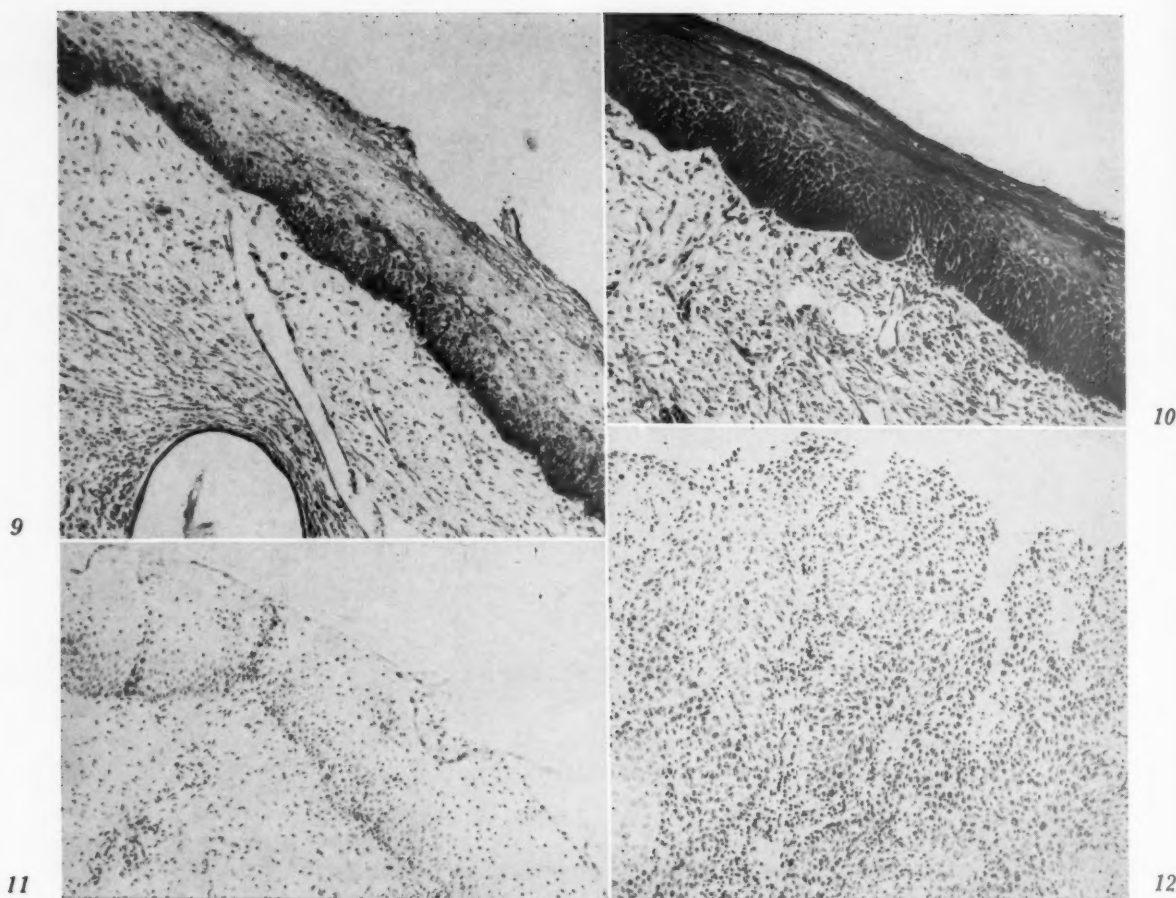


Fig. 9. The same photomicrograph as Fig. 8, but higher magnification. Normal part of the epithelium. (Methyl green-pyronin.  $\times 156$ ; reduced  $\frac{2}{5}$ .)

Fig. 10. The same photomicrograph as Fig. 8, but higher magnification. Increased reactions in the abnormal epithelium. (Methyl green-pyronin.  $\times 156$ ; reduced  $\frac{2}{5}$ .)

Fig. 11. Feulgen reaction. Normal cervix. ( $\times 140$ ; reduced  $\frac{2}{5}$ .)

Fig. 12. Feulgen reaction. Cancer of the cervix. Compared with normal tissue, nuclei are bigger and stained stronger. ( $\times 130$ ; reduced  $\frac{2}{5}$ .)

pH 7.4 was used as a substrate. Fast blue B salt added gives a black precipitate in locations of positive reaction. Compared with normal tissue, a marked quantitative increase of the reaction was noted in the cancerous epithelium (Figs. 29 and 30).

**Glucuronidase.** For the glucuronidase reaction short fixation in cold Formalin ( $4^{\circ}\text{C}$ . for 2 to 4 hours) was performed and frozen sections were cut. 8-Hydroxyquinoline glucuronide in acetone buffer pH 5.2 was used as substrate. This was coupled to the diazotate 4-benzoylamino-2:5-dimethoxyaniline. An orange red precipitate was formed in structures containing  $\beta$ -glucuronidase. Com-

pared with normal tissue, a marked quantitative increase of the reaction in cancerous epithelium was observed (Figs. 31 and 32).

#### Summary of results

Table I shows (in order of decreasing reactions) a summary of the histochemical characteristics in cancerous tissue as compared to normal tissue as displayed in the illustrations.

The enzymatic reactions all showed a quantitative increased reaction, especially the first four. Comparing normal and malignant tissue *macroscopically* after the reaction has taken place, one is able to distin-

Table I

*Nonenzymatic reactions.*

Markedly increased	RNA (Methyl green-pyronin)
Moderately increased	DNA (Feulgen)
Slightly increased	SH groups (Bennett)
Markedly decreased	SS groups (Methylene blue and CoS)
Markedly decreased	Glycogen (Best reaction)
Markedly decreased	Polysaccharides (PAS of McManus)

*Enzymatic reactions.*

Marked quantitative increase	Glucuronidase reaction
Marked quantitative increase	Esterase reaction
Marked quantitative increase	Phosphamidase reaction
Marked quantitative increase	Acid phosphatase reaction
Quantitative increase	Dehydrogenase reaction
Quantitative increase	Alkaline phosphatase

guish malignant tissue by the more intense color reactions. However, *microscopically* it is soon found that this increase is caused only by the larger amount of reacting epithelium in the malignant tissue. In a qualitative sense there is little difference in reaction intensity; the normal basal cells show an equal enzymatic staining quality as the cancer cells, but in cancerous tissue there are more undifferentiated cells.

**Comment**

The histochemical study of malignant cell tissues as compared to normal tissue is complicated by many factors. Even the thinnest

slides prepared with all necessary precautions of cutting, staining, and mounting show great variation in the staining take-up in the normal as well as the malignant tissues. Even the normal cervical epithelium shows difference in staining within the same stratified layer. Artifacts also can cause confusion. For example, staining may appear in places where it actually does not occur. This may happen by diffusion of staining material through blood vessels or through the basal cell membrane as in the alkaline phosphatase and glucuronidase reactions. Several specimens of tumor can yield a different amount of enzyme depending upon staining

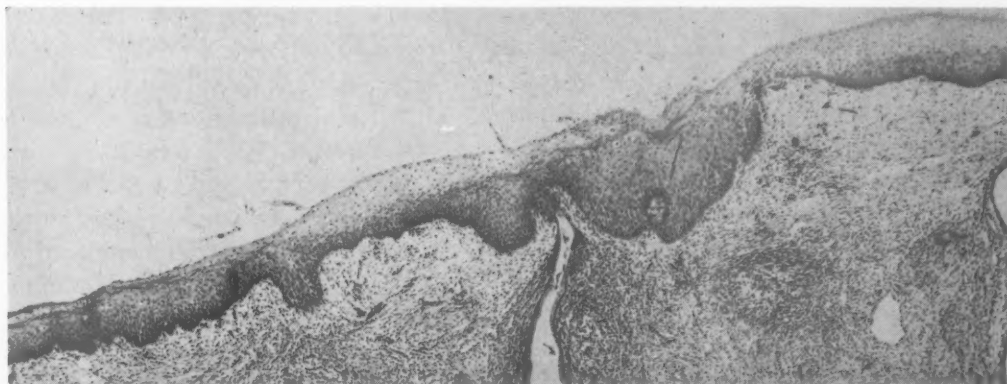
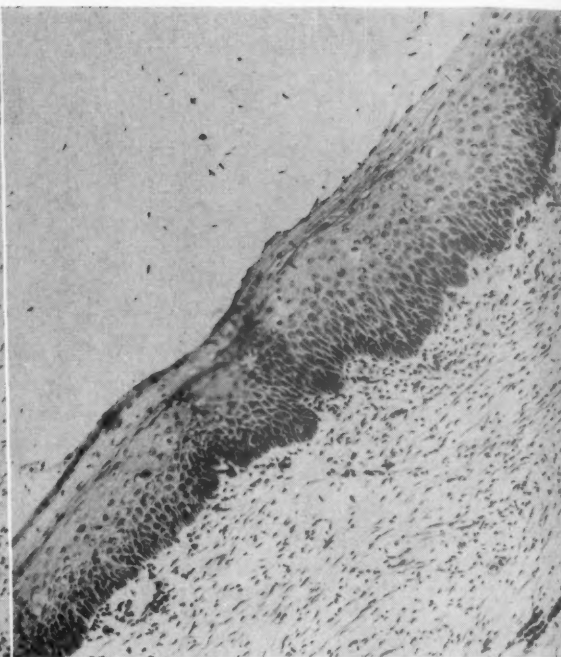


Fig. 13. Bennett reaction. Increase of the reaction in the abnormal epithelium (left). ( $\times 44$ ; reduced  $\frac{1}{6}$ .)





**Fig. 14.** Bennett reaction. The same photomicrograph as Fig. 13, but higher magnification. Normal part of the epithelium. It stains the basal cells, decreasing to the superficial epithelium. ( $\times 156$ ; reduced  $\frac{1}{3}$ .)



**Fig. 15.** Bennett reaction. The same photomicrograph as Fig. 13, but higher magnification. Stronger reaction in the abnormal part of the epithelium. ( $\times 156$ ; reduced  $\frac{1}{3}$ .)

take-up and the number of cells, as Greenstein and associates<sup>1</sup> demonstrated with cytochrome oxidase in thyroid adenoma and as was also observed by Rosenthal and Drabkin.<sup>2</sup>

Mounting with Permout in the nonenzymatic reactions does not give any difficulty, but the mounting of enzymatic reactions with glycerine jelly was accompanied by a constantly annoying air bubble formation which caused deterioration of the results. Dehydrating and mounting in balsam caused loss of stain probably due to alcohol and xylol mixtures, especially for the phosphatases.<sup>3</sup> We improved the results by diluting the glycerine jelly. Preparations often are no longer fit for use after a few weeks or months because of crystallization and precipitation of dyes, fading of dyes, and gas formations under the cover glass, probably caused by decomposition of diazotates adsorbed by the tissues with formation of nitrogen bubbles. This often necessitates repeated covering of the preparations with cover glasses.

The many contradicting viewpoints and conflicting results found in the literature concerning the histochemistry of malignant tissue must be founded for a great part on technical difficulties encountered in this work. It is necessary therefore always to include a section of normal tissue cut at equal thickness and size in the different staining procedures. It is an advantage to have normal and malignant cells of the same tissue together on one slide, even in one microscopic field. The macroscopic examination of the color intensity of the stained slides also played a role in the evaluation of differentiation of cancer and normal tissue. Two sets of comparisons were made: normal and cancer in situ tissue were compared on one slide and normal and invasive cancer were compared on another slide. The latter set sometimes showed greater differences.

Carbohydrates occur in 4 types: (1) the simple sugars built up of glucose molecules, such as glycogen in animal and starch in plant structures (reagent Best reaction); (2)



glycogen, polysaccharides, and mucoid substances, mucoid proteins, glycoproteins, chitin, hyaluronic acid, heparin, chondroitin, sulfuric acid (reagent PAS reaction); (3) glycolipids such as cerebroside, which on hydrolysis form a nitrogenous base (sphingosine) and a sugar; (4) nucleic acids, phosphoric esters of glucosides linked to purine, and pyridine bases (reagent Feulgen reaction).

Histochemically, sugars are usually demonstrated by their aldehydes. These aldehydes have to be liberated by oxidation as in the PAS reaction or by hydrolysis as in the Feulgen reaction. They change the chemical structure in the middle of the carbon chain  $\text{H}-\text{C}-\text{OH}$  to  $\text{H}-\text{C}=\text{O}$  breaking the carbon chain. In the case of the PAS reaction used for the second group of the above mentioned sugars, this occurs by oxidation, treating the tissue with periodic acid according to McManus,<sup>4</sup> or by lead tetra-acetate according to Criegee.<sup>5</sup> The resulting aldehydes linked to Schiff result in an intense red stain.

The PAS reaction is considered to be an

indication of the maturity of the cells.<sup>6</sup> In undifferentiated cells, whether normal basal cells or cancer cells, there is an absence of polysaccharides. This is correct as far as the basal and cancer cells are concerned, but not as far as the normal epithelium adjacent to the cancer cell layer is concerned. We invariably found the normal cell layer, immediately above the normal basal cells, rich in polysaccharides (right side of Fig. 5). However, the normal cell layer still present above the cancer cell layer (left side of Fig. 5) is poor or lacking in polysaccharides. This is in accordance with a higher quantitative glucuronidase reaction for cancer cells. Probably cancer cells consume a higher amount of polysaccharides necessary for their metabolism, which they acquire at the expense of the neighboring normal cells.

The difference between normal and cancerous tissue is sometimes better visualized by comparing normal and more advanced malignant tissue, sections taken of the same thickness and stained together in the same staining dishes. The normal tissue is abundant in PAS-positive material; in the super-

Fig. 16. SS reaction with methylene blue in normal cervix. Disulfide groups in the keratinized cell zone and some along the basal membrane. ( $\times 45$ ; reduced  $\frac{1}{5}$ .)



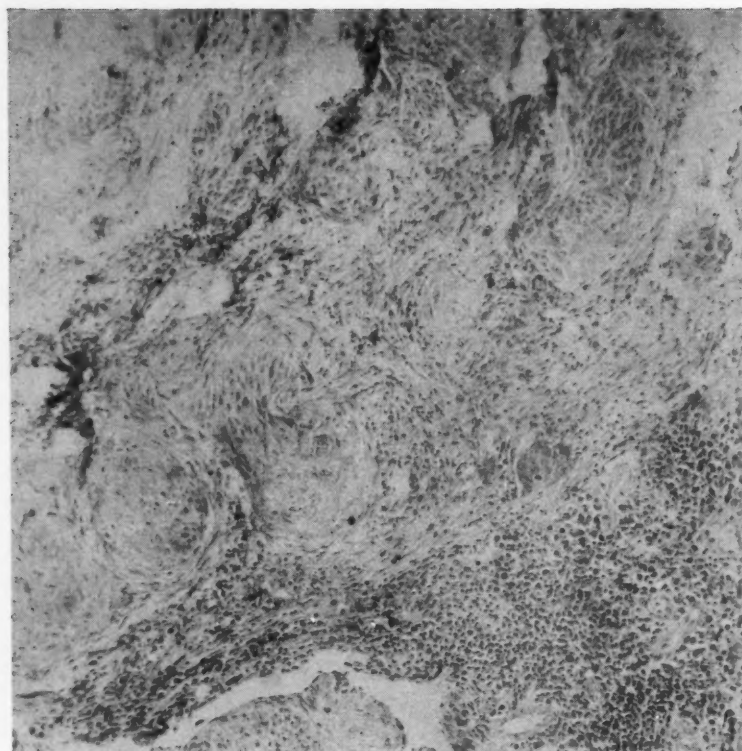
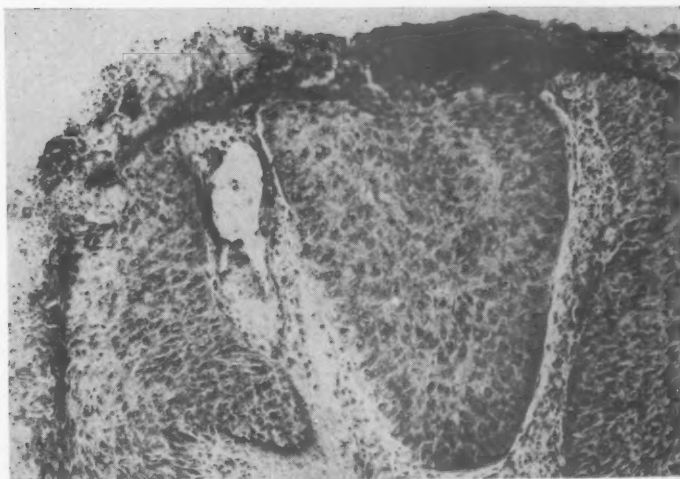


Fig. 17. SS reaction with methylene blue. No reaction in cervical cancer. ( $\times 130$ ; reduced  $\frac{1}{5}$ .)

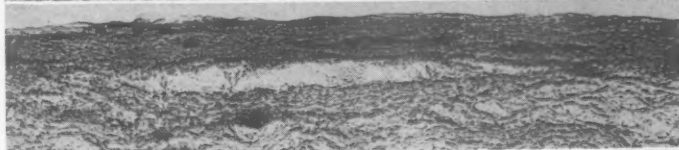


Fig. 18. SS reaction with cobalt sulfide. No reaction in cervical cancer. ( $\times 140$ ; reduced  $\frac{1}{5}$ .)

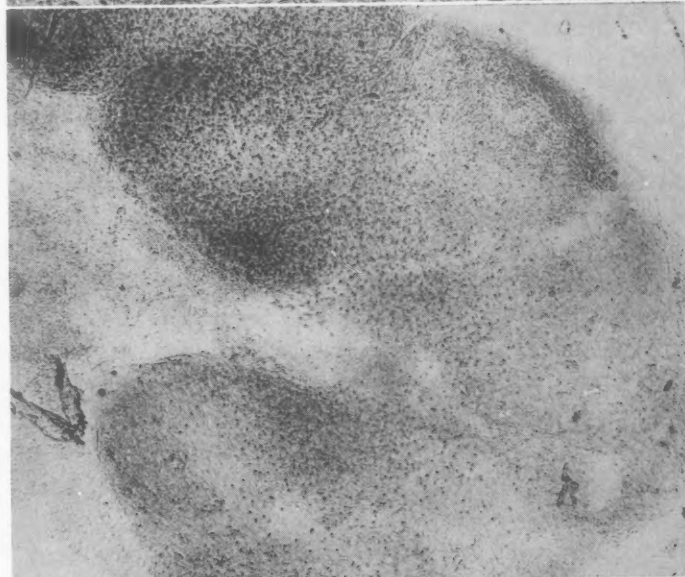
**Fig. 19.** Cancer of the cervix.  
Routine control. (Hematoxylin  
and eosin.  $\times 160$ ; reduced  $\frac{1}{4}$ .)



**Fig. 20.** Dehydrogenase reaction  
in normal epithelium.  
( $\times 130$ ; reduced  $\frac{1}{4}$ .)



**Fig. 21.** Dehydrogenase reaction  
in cancer of the cervix.  
No increase of the dehydro-  
genase reaction in cancerous  
tissue. Along the border of the  
penetrating cells a strong re-  
action. In the center of the  
epithelium sheets, a pale stain.  
Compared with normal tissue,  
the reaction in cancerous tissue  
is quantitatively stronger, qual-  
itatively the same. ( $\times 160$ ; re-  
duced  $\frac{1}{4}$ .)



**Fig. 22.** Alkaline phosphatase.  
Normal cervix. ( $\times 130$ ; reduced  
 $\frac{1}{4}$ .)



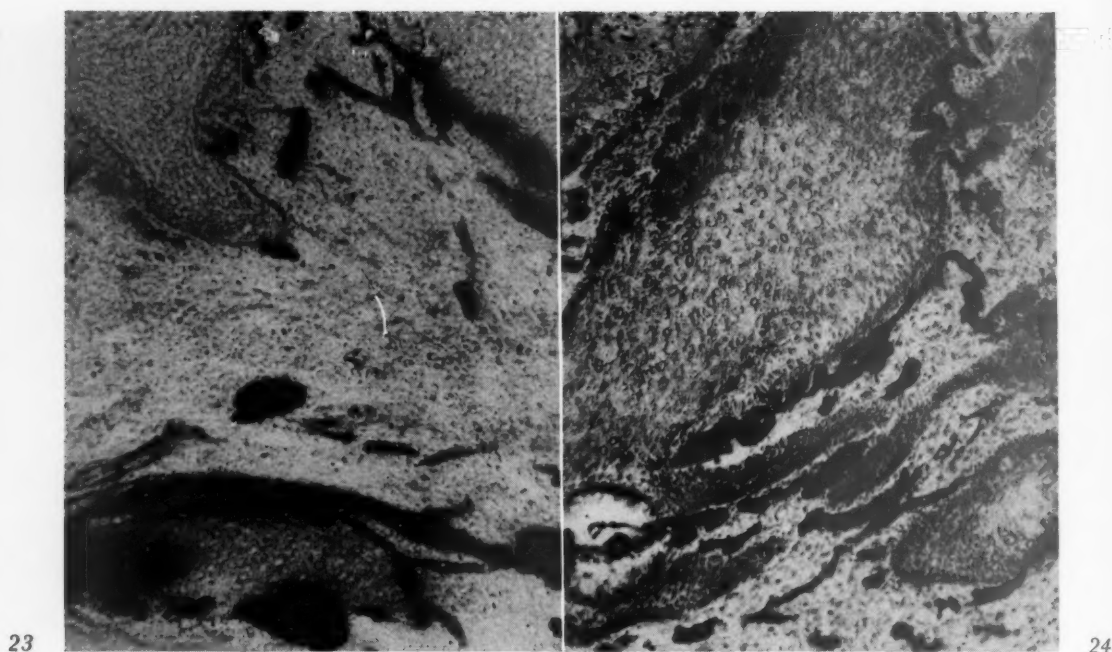


Fig. 23. Alkaline phosphatase. Cancer of the cervix. Quantitative but not qualitative increase of the reaction. The reaction is complicated by a strong activity of the endothelia of the blood vessels from where diffusion may occur. ( $\times 125$ ; reduced  $\frac{3}{5}$ .)

Fig. 24. The same case as Fig. 23, with hematoxylin counterstain. ( $\times 125$ ; reduced  $\frac{3}{5}$ .)

ficial cells of the squamous epithelium culminating here and there in dark red clumps. The endocervical glands containing mucoproteins show very much PAS-positive substance. The basal membrane and basal cells are devoid of staining material, as are blood vessels and the glycoproteins of the connective tissue. Malignant tissue treated in the same way shows a poor staining reaction throughout. Groups of malignant cells forming oval and round sheets also display a poor stain contrasting with the surrounding tissue. Nuclei are not stained.<sup>7</sup>

No microsections were digested by saliva, the reagent which removes glycogen from PAS-positive material. Mucin is not present in cervical squamous epithelium, and our attention was directed to squamous epithelium rather than the endocervical glands.

The oldest method for the demonstration of glycogen and starch is staining by iodine. Caventou<sup>8</sup> described it as early as 1826. Glycogen takes a brownish stain, starch a bluish. The degree of contrast is not high and because the preparations are not stable the reaction as a histochemical method has

become obsolete. However, it is still used as a practical gynecologic device (Schiller's test) to evaluate the lack of glycogen in cervical cancer and erosions. The Best<sup>9</sup> carmine is the method of choice for demonstration of glycogen. It stains also fibrin and mucin but with much less intensity.

In using the Best reaction, we find little or no glycogen in the basalis be it normal or cancerous. Again, the amount of glycogen in the normal superficial part of the epithelium (right in Fig. 2) is higher than the amount above the cancerous epithelium (left in Fig. 2) leading to the same conclusion as above. A negative Best reaction may be used as a possible recognition of cancer, as the Schiller test proves. At the same time it is clear that a noncancerous erosion also shows a negative Schiller test because of lack of superficial cells. In the Best reaction the sections were counterstained with hematoxylin because the blue stain differs so much from the carmine that confusion may be excluded.

When normal and cancerous tissue of the same thickness, prepared in exactly the



same way, are compared, the difference in the reaction is sometimes more pronounced. The normal tissue is abundant in carmine, increasing from the basal membrane to the superficial cell layers; the malignant tissue does not show any reaction. There is a distinct difference between the Best and PAS reaction in sections. The PAS color is much more intense and here and there shows dark red clumps. The increase in intensity from the basal to the superficial cell layers is intensified very quickly and extensively. The Best color is lighter and does not show clumps. The increase in intensity from the basal to the superficial layers is more gradual. The basal cell layers also show a small quantity of glycogen. The endocervical gland cells take no significant amount of the Best stain. The Best reaction does not stain nuclei.<sup>10</sup> Using the PAS technique, McManus and Findley reported in 1949 the absence of glycogen in cancer cells of carcinoma *in situ*.<sup>11</sup> Others confirmed their findings.<sup>12</sup>

The methyl green-pyronin reaction displays a blue stain with methyl green for DNA of nuclei and a red stain with pyronin for RNA of nucleolus and cytoplasm. Brachet<sup>13</sup> showed that the pyronin of the

Unna-Pappenheim mixture of methyl green-pyronin was an elective stain for RNA in both nucleolus and cytoplasm. Treated with ribonuclease, material stained red with pyronin was removable and considered to consist of RNA. He also showed that methyl green was an elective stain for DNA in chromatin not affected by ribonuclease.

The methyl green-pyronin mixture yields too pale a stain for usual histochemistry in our hands. A modified procedure, the Kurnick's method,<sup>14</sup> staining in methyl green in 0.2 M acetate buffer at pH 4.1, then blotting the slide, differentiating in *n*-butyl alcohol, and counterstaining with acetone saturated with pyronin, gave far better results.<sup>15</sup> Cytoplasm is red like the nucleoli, chromatin green. In order to remove the considerable amount of crystal violet present in the commercial methyl green, the watery solution is extracted with successive quantities of chloroform or amyl alcohol until the extracted fluid is colorless.

The methyl green-pyronin staining of the tissue showed a moderate staining of the cytoplasm (red) and nuclei (blue) in the normal basal layer as well as superficial epithelium with predominance of the methyl

Fig. 25. Acid phosphatase. Normal cervix. ( $\times 130$ ; reduced  $\frac{1}{3}$ .)

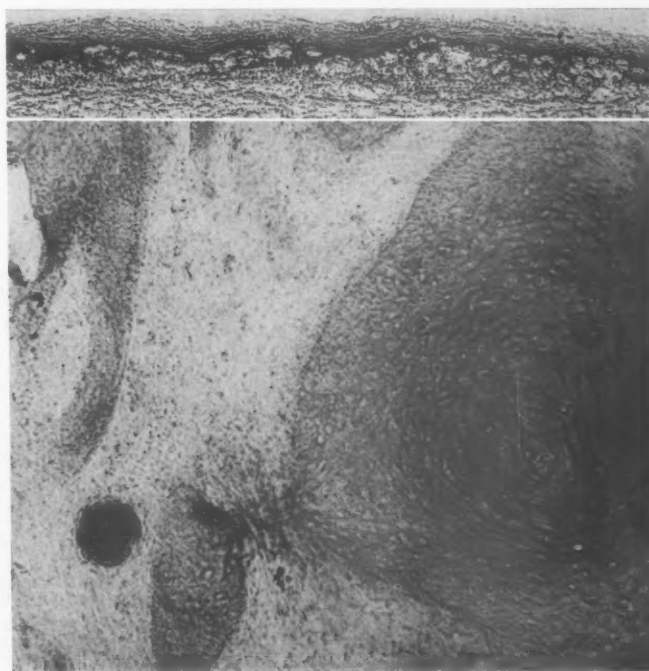


Fig. 26. Acid phosphatase. Cancer of the cervix. Comparing the acid phosphatase reaction of cancerous tissue with that of normal tissue, a marked quantitative increase is visible. Qualitatively there is no significant difference. ( $\times 125$ ; reduced  $\frac{1}{3}$ .)

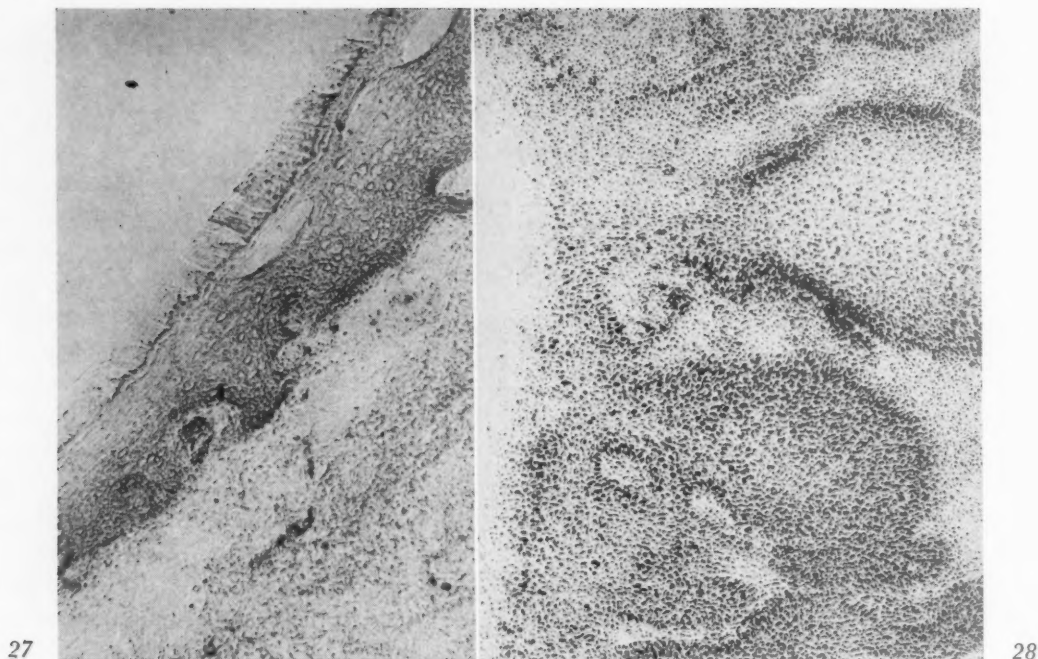


Fig. 27. Phosphamidase reaction. Normal cervix. ( $\times 125$ ; reduced  $\frac{1}{3}$ .)

Fig. 28. Phosphamidase reaction. Cancer of the cervix. Marked quantitative increase of the reaction. Qualitatively there is no significant difference compared with normal tissue. ( $\times 130$ ; reduced  $\frac{1}{3}$ .)

green staining of the normal basal cell structures. The stain is intensified in the cancerous tissue especially for the RNA of the cytoplasm. The malignant tissues display more intense staining of nuclei (blue) as well as cytoplasm (red), proving an increase in DNA and RNA, especially the latter. Pronounced is the larger though irregular size and intense staining of nuclei and the far more intense red staining of cytoplasm in the malignant tissue.

The Feulgen stain<sup>16, 17</sup> is based on the Schiff reaction for aldehydes. With this reaction, nuclei are stained, and cytoplasm and nucleoli remain unstained. The specificity of the Feulgen stain has been the subject of much discussion. Arguments against the specificity have been the assumption that there might be only adsorption of the stain by the nuclei without a real chemical reaction,<sup>18</sup> that the recoloration of the leukodye is due to nonaldehydic substances<sup>19</sup> and that Schiff stains products other than DNA, for example, histones<sup>20</sup> and chromosomin.<sup>21</sup> Recent studies, however, have made it very likely that the reaction is specific for

DNA. Especially the facts that without hydrolysis no Feulgen reaction occurs, that the reaction can be impeded by the enzyme DNase, and that the reaction can be prevented by specific blocking reagents<sup>22</sup> such as carbonyl reagents makes specificity highly probable. Moreover, Feulgen stains isolated chromatin threads<sup>23, 24</sup> and there exists an excellent agreement between the Feulgen stain and ultraviolet spectrophotometry.<sup>25</sup> Stowell and Cooper<sup>26</sup> examined by a modified Feulgen reaction the amount of DNA in normal and neoplastic tissue by photometric recordings.

In our preparations there was a moderate increase of DNA when the cancerous and the normal tissues were compared. Simple macroscopic comparison of the slides shows a more intense stain in the malignant tissue. Microscopic examination showed an intensified staining of the malignant tissue. This was manifested more by the size of the nucleus than by the intensity of the stain. However, small malignant nuclei also show a very strong reaction. The red Feulgen color has a different character from the red

Best and PAS stains. The color, magenta red, has a purple tendency in the Feulgen-positive material. Generally, Feulgen does not stain the cytoplasm of the cell. Some red particles as either dust or mitochondria are visible in the cytoplasm sometimes.

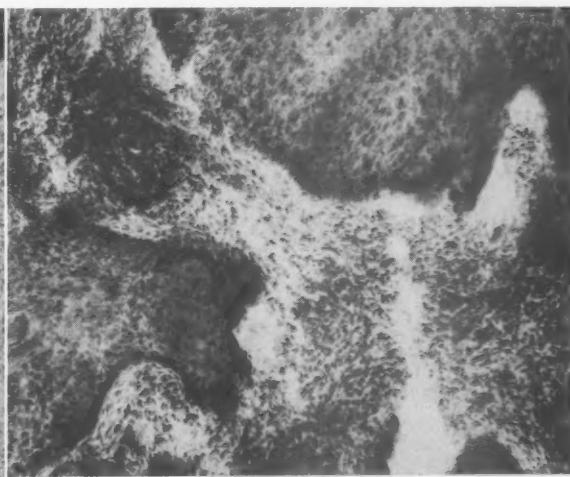
Sulfur-containing groups are present in animal tissue bound to amino acids. Glutathion is the only uncombined compound, but diffusible so that its localization is unknown. The other sulfur compounds such as cysteine and methionine are bound to protein molecules. Sulfhydryl compounds are reducing agents. They are contained in the germinal layers of the squamous epithelium of skin and cervix. Their oxidation products, the disulfides, are found in the more superficial keratin layers. Bromobenzene<sup>27</sup> and dibasic acids<sup>28</sup> such as maleic and citraconic acid decrease the effect of some carcinogens on the skin. Bromobenzene probably interferes with the sulfur metabolism, resulting in a lowering of the sulfur levels of the skin and a lesser potentiality for malignant disease. The inhibition by mustard gas of the formation of tar tumors<sup>29</sup> can be explained in the same way. The inhibitors probably compete successfully with the carcinogens in reacting with the sulfhydryls.<sup>30, 31</sup>

Bennett<sup>32</sup> was able to locate SH groups in regions formerly known to contain SH groups by the nitroprusside reaction, such as nerve cell bodies, red blood cells, capillary endothelia, and retinal rods. In our tissue sections the reaction appeared as an orange stain in the basal membranes and basal cells decreasing to the surface. Strong reaction in the blood vessels was noted. The reaction was stronger in the cancerous tissue than in the noncancerous due to the greater amount of undifferentiated cells. The intensity of the reaction was also slightly increased.

Methods for SS groups are based on the cleaving of the disulfide bonds of cystine. The resulting cysteic acid can be demonstrated by staining with dilute aqueous solutions of methylene blue at low pH or combination with cobalt salts, forming black cobalt sulfide. Both reactions were used and showed identical localization of both black and blue stains in the superficial cell layers of the cervix. Keratin masses in squamous cell carcinoma are strongly stained. According to Pearse,<sup>33</sup> the methylene blue method is more specific than other methods for examination of sulfur-containing products. Lillie<sup>34</sup> reports that periodic acid and bromine in carbon tetrachloride can also be



29



30

Fig. 29. Esterase reaction. Normal cervix. Pronounced activity. ( $\times 125$ ; reduced  $\frac{2}{3}$ .)

Fig. 30. Esterase reaction with hematoxylin counterstaining. Cancer of the cervix. Marked quantitative increase of the reaction as compared with normal tissue. Qualitatively there is no increase as the reaction in normal epithelium may also be very marked. ( $\times 125$ ; reduced  $\frac{2}{3}$ .)



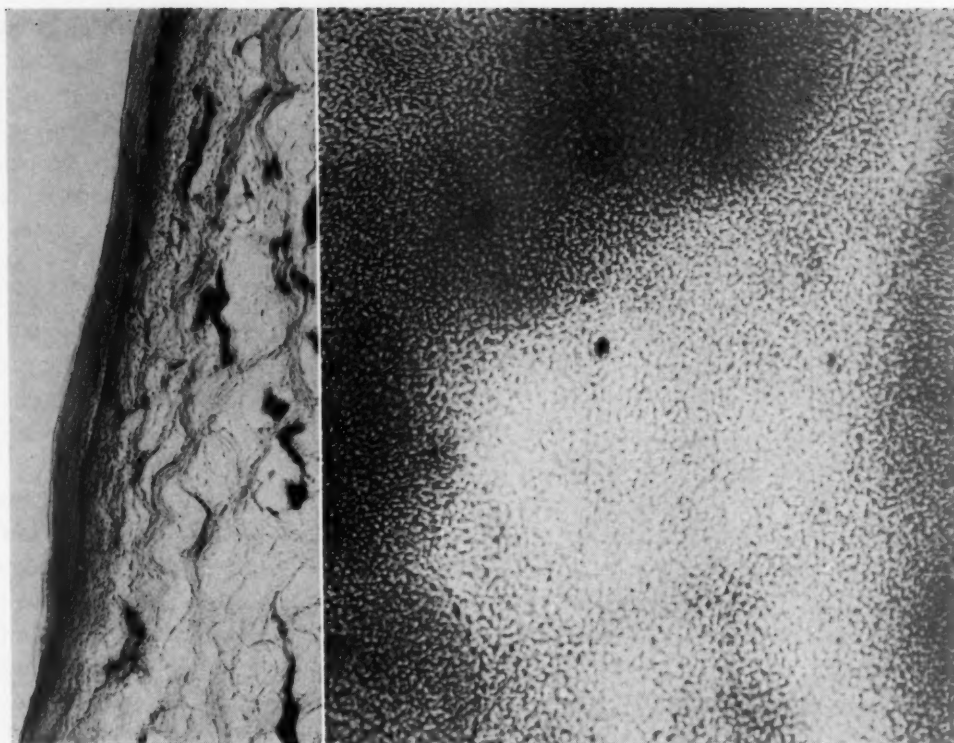


Fig. 31. Glucuronidase reaction. Normal cervix. ( $\times 140$ ; reduced  $\frac{1}{4}$ .)

Fig. 32. Glucuronidase reaction. Cancer of the cervix. When the glucuronidase reaction of cancerous tissue is compared with that of normal tissue, marked quantitative increase of the reaction is visible. Qualitatively there is no significant difference, although this enzyme in cancer may often surpass the normal cervix in intensity. ( $\times 140$ ; reduced  $\frac{1}{4}$ .)

used as oxidants. Barnett and Seligman<sup>35</sup> developed a new method for the demonstration of sulfhydryl and disulfide groups using dihydroxydinaphthyl disulfide and diazo blue B.

We found that sheets of cancer cells in round or oval groups showed a far lower degree of staining than the normal squamous epithelium and as such our results agreed with those of Foraker.<sup>39</sup> Sulfhydryl and SS groups are present mainly in the cytoplasm of the cell.

For enzymatic reactions even more than for nonenzymatic procedures nonmalignant tissues have to accompany the malignant in order to prove the experimental results. Enzymes are much more vulnerable to chemical reactions and high temperatures, and the tissue has to be more fresh. We tried both paraffin embedding and cutting frozen sections, and abandoned the first

method because it destroyed too much of the enzyme activity. Fixation in Formalin or acetone at low temperature was applied, some enzymes like dehydrogenase and the phosphatases resisting acetone better than Formalin. The enzymes belong to two groups, the oxidative and the hydrolytic.

Dehydrogenases belong to the oxidative enzymes and play an important role in the respiratory processes of many cells. They transfer hydrogen to an acceptor. They are easily damaged by any fixative and require treatment by frozen section, embedding destroying their activity. The principle of their demonstration is the changes in color of the hydrogen acceptor when reduced. There are 3 compounds used for their demonstration, methylene blue, tetrazolium compounds, and tellurites. The methylene blue method is very useful for the demonstration in vitro of the amount of dehydrogenase in tissue. For mi-



microscopic work, however, the methylene blue technique is not practical because a negative stain gives a poor localization and the method is complicated by the fact that it must occur under anaerobic conditions to prevent oxidation by the atmosphere. The tellurite<sup>36</sup> method is less sensitive. Dehydrogenase has been found in heart, kidney, pancreas, thyroid, uterus, adrenals, and vagina. Glick and Nayyar<sup>37</sup> examined the quantity of dehydrogenase in the adrenal gland of the steer by the method of Pearson and Defendi<sup>38</sup> who used 2(p-iodophenyl)-3-(p-nitrophenyl)-5-phenyl tetrazolium chloride as the substance to be reduced. Foraker<sup>39</sup> compared sulfhydryl, dehydrogenase activity, nuclear size, and hyperchromatism in malignant tissue and found their values well proportioned.

We used the neotetrazolium method<sup>40</sup> giving good localization of the formed formazan and a distinct color range. The sites of high enzymatic activity in our preparations showed deposits of a dark blue pigment (diformazan), those of lower activity stained red (monoformazan). The blue pigment formation is limited to the basal membrane and basal cells and decreases to the surface. The reaction occurs in the cytoplasm of the cell. Comparing the normal basal layer with cancerous tissue we found microscopically not much difference in reaction. Where the cancerous tissue consisted of many layers there was a decrease of reaction in the center of the growing cell sheets. Macroscopic examination of the microslides revealed a stronger reaction in cancer because there are more undifferentiated cells, as already stated. Wingo and associates<sup>41</sup> found in general a similar distribution pattern for dehydrogenase activity and sulfhydryl reaction. We found the same with a slight increase for the sulfhydryl reaction.

The phosphatases belong to the hydrolytic enzymes. They hydrolyze esters resulting in phenols, which coupled to diazotates form dyes. The Gomori<sup>42</sup> method for alkaline phosphatase is based on the demonstrations of acids by precipitation with calcium, forming insoluble calcium phosphate, trans-

formed by cobalt nitrate to black cobalt sulfide. Alkaline phosphatase is found in the liver, kidney, intestinal mucosa, endometrium, ovary, salivary glands, endothelia of blood vessels, and pancreas. Woodard<sup>43</sup> found an increase of alkaline phosphatase in hepatoma of the rat in comparison with the normal liver. Allen and Slater<sup>44</sup> examined the influence of hormones upon the distribution of alkaline phosphatase in mouse adrenal cortex.

We used a method originally described by Menten,<sup>45</sup> later modified by Gomori,<sup>46</sup> where a sodium naphthyl phosphate is coupled to a diazonium salt forming an insoluble black dye. We found the reaction in our preparations of questionable nature. Although there was macroscopically some quantitative increase in the malignant as compared with normal tissue, microscopically the reaction was variable and was complicated by the very strong reaction of the blood vessels from which diffusion might occur into the surrounding tissue. Staining took place only in the cytoplasm. No nuclear reaction was noted.<sup>46, 47</sup> Increased alkaline phosphatase activity has been described in malignancies of liver<sup>48</sup> and testes.<sup>49</sup>

Acid phosphatase is found in red blood cells, kidneys, and especially in the prostate. Gomori,<sup>50</sup> comparing his lead sulfide method with the Rutenburg and Seligman method,<sup>51</sup> found differences which appear to be due partly to the presence of more than one acid phosphatase in the tissues, partly to diffusion artifact. Results of techniques should be interpreted with caution. Burton<sup>52</sup> described a method for acid phosphatase examination using tetrazotized dianisidine (Brentamine Fast Blue B).

We used a modification of the Seligman-Manheimer method described by Grogg and Pearse<sup>53</sup> using sodium  $\alpha$ -naphthyl phosphate and fast blue B salt at pH 5. It showed a quantitative increased reaction in cancerous tissue in comparison with normal tissue but under the microscope cancer cells behave like basal cells and there was no significant difference. Cytoplasm is stained but there is a questionable nuclear reaction. Most

authors describe an increased acid phosphatase activity of malignant tissues such as in stomach, breast, skin, prostate, and bone cancers.<sup>54-57</sup>

Phosphamidase was discovered by Gomori<sup>58</sup> as a specific enzyme when he compared the localization of his substrate p-chloranilidophosphonic acid at pH 9 and pH 5. The very different picture was a strong indication for a separate specific enzyme. The method of examination is, except for the substrate, almost identical with the lead sulfide method of Gomori for acid phosphatase. The enzyme hydrolyses nitrogen-phosphate bonds and is probably a specific acid phosphatase although Pearse<sup>59</sup> doubts its specificity. Occasionally failures are experienced, such as nonspecific impregnation and artifacts. For the most part the enzyme is present in the cytoplasm. Some is visible also in the nucleus. According to Gomori<sup>58</sup> moderate amounts are present in liver, renal tubules, adrenal cortex, small intestines, bronchi, and pancreas. He found a strong reaction in gray matter of the central nervous system (especially cerebellum) and in malignant tumors, and the intensity of the reaction was in accordance with the degree of histologic malignancy. Some other examiners, such as Pearse<sup>59</sup> and Gross,<sup>6</sup> found none or variable results. We found a significant increase in cancerous as compared with normal tissue but only in a quantitative sense. Qualitatively cancer cells behaved as basal cells, and there was no significant difference in staining quality.

The first azo dye technique for esterase was published in 1949 by Nachlas and Seligman.<sup>60</sup> The principle was enzymatic hydrolysis of  $\beta$ -naphthyl acetate in the presence of diazonium salt. The method produced artifacts and was successfully modified by Gomori<sup>61</sup> who used  $\alpha$ -naphthyl acetate instead of the  $\beta$ -salt and found the right pH and temperature to perform the reaction. Esterase is abundant in pancreas, serum, liver, kidney, intestinal mucosa, testis, and central nervous system. It is found also in the conduction system of the heart.<sup>62</sup> We found it, with glucuronidase, quantitatively the

strongest reaction in differentiating normal from cancerous tissue. It stains with a black precipitate the normal basal membrane but is intensified along the border of the penetrating cancer cells and does not show a paler stain in the center of the penetrating epithelial sheets. The enzyme is present in the cytoplasm of the cell; nuclei are negative. Qualitatively, again the difference in staining quality in comparison with normal basal cells is only slight or nonexistent. Cohen and Seligman<sup>63</sup> found that in general cancers had less esterase activity than the corresponding normal tissue. Gross<sup>6</sup> found higher activity in cervical cancers.

Glucuronidase is an enzyme which Fishman and his associates<sup>64</sup> have found plays an important role in detoxication processes in the metabolism and urinary excretion of phenolic compounds and in the metabolism of steroid hormones. Fishman and Baker<sup>65</sup> found the enzyme in the Purkinje cells, pancreatic islet cells, endometrium, liver, and renal cortex. The enzyme is present mainly in the cytoplasm. In malignant tissues it is often found in high concentrations.<sup>66, 67</sup> It is also present in high amounts in tissues exposed to estrogen stimulation.<sup>64</sup> Cyclic changes of enzyme activity in the endometrium are in accordance with the titers of blood and urinary estrogens during the menstrual cycle.<sup>67</sup> Kerr, Campbell, and Levvy<sup>68</sup> showed that uterine  $\beta$ -glucuronidase is an index for the growth of liver and kidney. An interesting observation is that venous blood leaving a tumor contains less glucose than does venous blood in a tumor-free location of the same animal.<sup>69</sup> Crabtree<sup>70</sup> found a high glycolysis in tumor tissue and Cori<sup>71</sup> showed that the amount of lactic acid in mouse mammary carcinoma rose after glucose administration, all facts pointing to the close connection of tumor and glycogen metabolism. Seligman<sup>72</sup> developed a reaction with the synthetic substrate 6-bromo-2-naphthyl  $\beta$ -D-glucopyruonoside. The method of Friedenwald and Becker<sup>73</sup> is mostly used for examination of the glucuronidase reaction. The method depends upon the hydrolysis of 8-hydroxyquinoline glucuronide

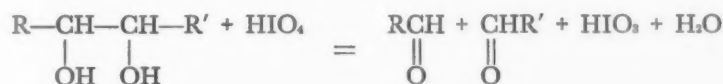
in the presence of a ferric salt. In positive reactions the resulting precipitate of ferric hydroxyquinoline is converted to Prussian blue by acid ferrocyanide forming a greenish-black pigment.

In using this method we experienced lack of localization due to great diffusibility of the employed chemicals which is the reason that we changed to the 8-hydroxyquinoline method of Pearse<sup>74</sup> which is simpler and which gave excellent results in our hands. With this method the resulting hydroxyquinoline is coupled to the diazo dye 4-benzoylamino-2:5-dimethoxyaniline (diazo fast blue RR), giving an orange precipitate in sites of positive reaction. We found glucuronidase with esterase the strongest reaction in differentiating normal from cancerous tissue. In moderate degree it stains with an orange precipitate the normal basal membrane, but is intensified along the border of the penetrating cancer cells and does not show paler staining in the center of the penetrating epithelial sheets. Here again the difference is only quantitative and can be seen by simply looking at the slide without microscope. Observed under magnification, however, cancer cells look like basal cells according to color intensity.

#### Staining techniques and chemistry

The Best-glycogen reaction is based on the staining by carmine of glycogen in its different concentrations. The cytoplasm of the cell is stained. The nuclei are unstained and may be colored by hematoxylin as contrast stain.

The nature of the chemistry of periodic acid-Schiff reaction (PAS) can be understood by an oxidation of glycol groups to produce aldehyde groups as follows:



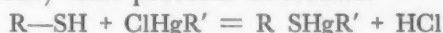
For amino alcohols ( $\text{R}-\text{CH}-\text{CH}-\text{R}'$ ) comparable reactions are described.

$$\begin{array}{c} | \quad | \\ \text{OH} \quad \text{NH}_2 \end{array}$$

The methyl green-pyronin staining is based on the affinity of nucleic acids for methyl green and pyronin and is a function of their state of polymerization.<sup>15</sup>

The Feulgen reaction is based on the Schiff reaction for the aldehyde desoxyribose formed by acid hydrolysis from nucleoproteins.

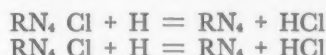
The mercurial method for sulfhydryl groups (groups of cysteine combined in various proteins) of Bennett is based on the reaction of mercaptans with SH groups. The synthesized 1-(4-chloromercuriphenylazo) 2-naphthol or red sulfhydryl reagent (RSR) can be represented by the formula  $\text{ClHgR}'$ ; the reaction with SH groups ( $\text{R-SH}$ ) then proceeds as follows:



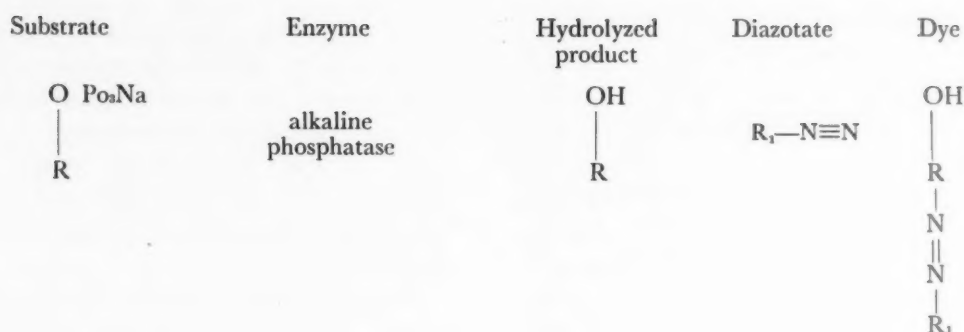
Reaction methods for SS (disulfide groups) consist of reduction methods by potassium cyanide or oxidation methods with performic and peracetic acid. We performed the peracetic acid method and stained with methylene blue at low pH and with cobalt sulfide.

For the examination of succinic dehydrogenase activity we made use of the observation of Rosa<sup>75</sup> that phosphate buffer at pH 8.2 and the incorporation of sodium cyanide into the incubating medium as an effective blocking agent for cytochrome oxidase improves the reaction.

Sodium succinate is used as the substrate (hydrogen donor) and neotetrazolium chloride as the reagent to be reduced. Depending on the intensity of the reduction, monoformazan (red) or diformazan (blue) is formed as follows: Neotetrazolium chloride + H = mono- or diformazan.







The chemical foundation of enzymatic hydrolysis is based on the formation of a phenol coupled to a stable diazo salt.

For other enzymes and diazotates comparable reactions take place.

The enzymatic hydrolysis and coupling occurring at the same time with formation of an insoluble dye are known as simultaneous coupling azo dye methods in contrast to the postcoupling azo dye methods where the incubation with the substrate and coupling to the dye occur as separate reactions. The simultaneous method proved to be of the greatest importance and was the only one applied by us. For a good result it is necessary that the formed phenol at the place of enzyme activity is precipitated as quickly as possible as an insoluble dye without displacement or diffusion, causing artifacts, mostly due to coupling which occurs too slowly or is incomplete. The speed of reaction is especially dependent upon a pH fit for the reaction in question. An acceleration of the coupling may also occur by reason of increase of temperature, increase of diazotate concentration, decrease of acidity of the fluid medium and by addition of certain activators, for example, magnesium, pyridin, etc. The concentration of both phenols and diazotates is important for a good result and because the diazotate concentration cannot be unduly high, which would impede the reaction, it is possible that in cases of high enzymatic activity and formation of phenols not sufficient diazotate is present in the fluid. In such cases it may be of advantage to promote an energetic me-

chanic movement in the fluid to counteract local concentration shortages of diazotates. Naphthol-As-esters, where on the third place a naphtholic anilid is added, are generally to be favored above the simple naphthol esters because of greater exactness of dye precipitate. They were applied by us as an esterase method and gave good cytologic localization. However, they require an exact pH of 7 and are sensitive to pH changes. Azo dyes do not stain the nucleus of the cells, with the exception perhaps of the phosphamidase reaction. This is in contrast with biochemical experience with isolated cell nuclei. The question has arisen whether this negative result is due to factors of permeability of the cell wall or unfitness of the dyes to penetrate the nuclear membranes.

In using azo dye techniques there are no general rules for proportions of substrates and dyes. These must first be found out experimentally, and the dosage depends upon the enzyme activity of the tissue in use. If the azo dye is too high in concentration in comparison with enzyme activity, inhibition of enzyme activity is the result. If the azo dye is too low in concentration then artifacts of insoluble dye precipitates occur, the necessary coupling component not being present. In general the best results are obtained by concentration of 1 mg. per cubic centimeter for azo dye and half of this concentration for substrate.

An interesting chemical characteristic is found in some diazo dyes containing two reactive diazo groups like fast blue salt B. At pH 5, where only one diazo group is active,



a red color prevails. At pH 9.2, where apparently both groups are active, a black dye is formed.

The best temperature for enzyme reactions is usually 37° C., but reactions for enzyme activity are often performed at room temperature 15 to 20° C. to prevent decomposition of azo dyes. Especially in esterase, the reaction occurs so quickly that lowering of optimum temperature for enzyme activity is necessary to prevent too extensive a production of naphthol hydrolysis with artifact formation. Phosphatases probably play an important role in carbohydrate and nucleic acid metabolism. The fact that they are present at border lines of cell membranes and blood vessels may indicate that they are active in transport between these structures.

Esterases are of importance for metabolism of fat and proteins. In many organs a specific enzyme build-up has been shown. For example, in the Langerhans islands of the rat pancreas, esterase activity has been formed in the A cells, at the periphery of the organ. Acid phosphatase in the B cells is found in the center of the islands. By experimental alloxan diabetes in animals with specific B cell damage, the activity of acid phosphatase has been shown to be destroyed. At the same time the esterase activity of the peripheral A cells stays intact. In experimental pathology, enzyme activity gives interesting data. Epithelioid cells and giant histiocytes in mice and rats resistant to tuberculosis show strong activity in acid phosphatase. The same in man show strong activity in esterase. Both reactions in guinea pigs very susceptible for tuberculosis are negative. In this way it is possible that enzyme histochemistry may become an important branch of science because knowledge of enzymatic connections may establish functional understanding beyond the morphologic structures, in a sense histology and physiology in one field.<sup>76</sup>

### Conclusion

1. Twelve histochemical reactions have been applied to normal and malignant tis-

sue—6 nonenzymatic, 6 enzymatic.

2. Although some of the nonenzymatic cytochemical differences may be ascribed to immaturity of the cancer cells not different from normal basal cells, there appear to be chemical differences specific for malignant cells. We believe that an increased RNA content of the cytoplasm of the cell, an irregular but usually increased DNA content of the nucleus, a decreased glycogen and polysaccharide content together with a slightly increased SH belong to the characteristics of cervical cancer cells in comparison with normal cells.

3. The oxidative enzyme dehydrogenase was explored with the neotetrazolium method. The hydrolytic enzymes, phosphatase, esterase, phosphamidase and glucuronidase were explored with diazo dyes. The neotetrazolium method uses transport of hydrogen to an acceptor showing distinct color ranges depending on the intensity of reduction. The hydrolytic enzymes originate in the formation of insoluble precipitates in places of enzyme activity of phenols formed by hydrolysis of the substrate and azo dyes coupled to them. For optimum activity, concentration of substrate and azo dye, pH, temperature, solubility, and time of incubation are of primary importance and must be established experimentally. Different enzymes require different fixatives.

4. Although all the enzymatic reactions used by us showed a quantitative increase of the reaction in malignant tissue (alkaline phosphatase and dehydrogenase only in a minor way) making the differentiation of cancer already possible with the naked eye compared with normal tissue, microscopically there was no absolute criterion found to distinguish malignant cells from normal ones. Glucuronidase, esterase, phosphamidase, and acid phosphatase showed strong reactions, but the normal basal epithelium in most cases showed the same. Because of unintentional differences in color intensity met in enzymatic work, it is always necessary to expose both normal and malignant tissue in the same way and at the same time for comparison.

5. The presence of enzymes in the normal organs and their localization in pathologic conditions may form the basis for organic enzyme patterns where functional activities are seen in morphologic relation.

I wish to express my appreciation to Dr. Ferguson, Department of Obstetrics and Gynecology,

for obtaining cervical material, Miss Kern for technical preparation of tissue, Miss Herman for obtaining necessary references, and Dr. Max Millard, Department of Pathology for grammatical corrections.

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# Carcinoma in situ of the cervix and adenocarcinoma of the endometrium

## Report of a case

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IT IS unusual for multiple primary malignant tumors to occur in a single organ. Relatively few such tumors of the female genital tract have been reported in the past 25 years. When consideration is limited to multiple primary carcinomas of the uterus, the frequency is even less.

Adenocarcinoma of the endometrium in combination with adenocarcinoma of the cervix has been observed in 3 cases.<sup>1, 2</sup> Twelve instances of adenocarcinoma of the endometrium and invasive carcinoma of the cervix have been reported.<sup>1-8</sup> Involvement of the same uterus with carcinoma, sarcoma and invasive carcinoma of the cervix has been verified in 2 cases.<sup>9, 10</sup> A survey of the literature revealed no report of adenocarcinoma of the endometrium and carcinoma in situ of the cervix.

The possibility of direct extension or metastasis from another tumor must be eliminated before 2 malignant neoplasms in the same organ can be diagnosed as separate primary tumors. Each tumor, therefore, must possess distinct morphological characteristics, arise in different situations, and grow independently. The following case is presented as one double primary uterine carcinoma, the above criteria having been fulfilled.

A 59-year-old Spanish-American woman, gravida vi, para iv, who had had 2 abortions, was admitted to the Bernalillo County-Indian

Hospital on April 10, 1958, because of postmenopausal bleeding. The menopause occurred at the age of 50 years. On April 7, 1958, sudden, severe vaginal bleeding began and continued in lesser amounts until her admission to the hospital.

Pelvic examination revealed a senile atrophic vaginal mucosa and no signs of recent bleeding. The cervix was smooth. The uterus was ante-flexed, slightly enlarged, and nontender. The adnexa were normal. Laboratory and x-ray findings were within normal limits. On April 13, a cone cervical biopsy, followed by dilatation and curettage of the endometrium, was performed under general anesthesia.

The histopathological examination revealed extensive, chronic inflammation of the cervix with extreme squamous metaplasia and, in some regions, areas of carcinoma in situ with some invasion of the endocervical glands (Fig. 1). A section of the endometrium showed an infiltrating Grade I adenocarcinoma (Fig. 2).

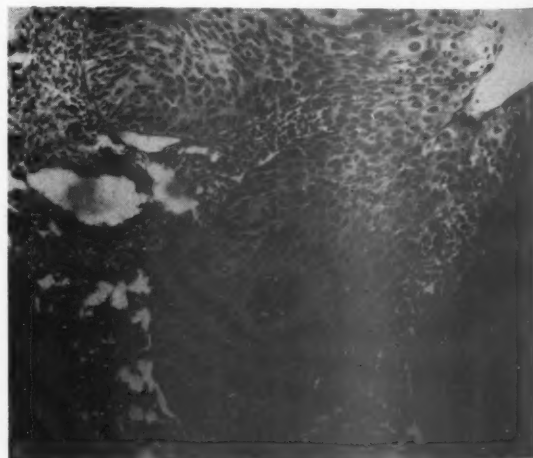


Fig. 1. Carcinoma in situ of cervix.

*From the Department of Gynecology of the Bernalillo County-Indian Hospital, Albuquerque, New Mexico.*



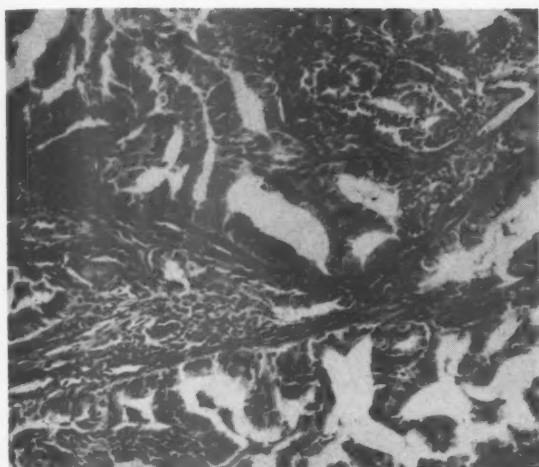


Fig. 2. Adenocarcinoma of the endometrium.

On April 18, 90 mg. of radium in Ernst applicators was applied for a 72 hour period. The patient was advised to return in 6 weeks for a hysterectomy followed by cobalt therapy. However, she refused any further treatment. A release of responsibility was signed and the patient has not been seen since.

### Summary

A case is reported of 2 simultaneously occurring carcinomas of the uterus, one a carcinoma in situ of the cervix and one an adenocarcinoma of the endometrium.

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# Endometriosis of the vermiform appendix

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EXTERNAL endometriosis involving the appendix may produce a clinical syndrome necessitating primary surgical removal of the appendix. One third of the patients seen at the St. Luke's Hospital with a pathological diagnosis of appendiceal endometriosis had a primary appendectomy performed because of a clinical diagnosis of acute or recurrent appendicitis. The majority of those appendices did not reveal any pathological evidence of inflammation. One may conclude from these observations that endometriosis of the appendix may be considered in the differential diagnosis of right lower quadrant pain in the sexually mature female.

External endometriosis involving the vermiform appendix is being encountered with increasing frequency; however, the fact remains that the vermiform appendix continues to be the least common site for external endometriosis in viscera located in or near the pelvic cavity. Sampson<sup>1</sup> in 1922 described 12 cases of intestinal endometriosis. Four of those involved the appendix. Dougal<sup>2</sup> in 1923 described an "adenomyoma involving the vermiform appendix." Outerbridge,<sup>3</sup> stimulated by Sampson's report on "intestinal adenomas of the endometrial type," published an article in 1925 describing 4 cases of "cystic lesions of possible endometrial origin in the appendix." Outerbridge cited Dougal's case and commented on the paucity of reports of appendiceal endome-

triosis in the literature. Collins<sup>4</sup> reported 125 cases of endometriosis involving the vermiform appendix in the world literature from 1860 through 1951. He added 9 cases of his own. Sutton and Hardy<sup>5</sup> in 1952 reported 15 cases of appendiceal endometriosis occurring in 6,911 appendices removed in 3 hospitals in St. Louis during the years 1940-1952. Romanus<sup>6</sup> reported 5 cases of appendiceal endometriosis and stated that Collins failed to include 11 cases from the world literature. Subsequent reports by Senapati,<sup>7</sup> Gardner and associates,<sup>8</sup> Cabaud,<sup>9</sup> Pecori,<sup>10</sup> and Limage<sup>11</sup> have brought to 170 the number of cases of appendiceal endometriosis reported in the world literature through 1955. In a study of 50,000 specimens of the human vermiform appendix, Collins<sup>12</sup> reported endometriosis present in 0.054 per cent.

Appendiceal endometriosis is infrequently associated with endometriosis of the reproductive organs. Smith,<sup>13</sup> Hayden,<sup>14</sup> Thierstein and Allen,<sup>15</sup> and Scott and Te Linde<sup>16</sup> have reported the following incidences of this lesion of the appendix among cases of pelvic endometriosis: 1:159, 1:569, 2:866, and 7:516, respectively. By virtue of the proximity of the appendix to the pelvic viscera, one would expect to find the appendix involved with greater frequency than the above figures indicate, if Sampson's theory of histogenesis of external endometriosis is correct.

## Materials

Thirty cases of pathologically proved endometriosis of the vermiform appendix were diagnosed at the St. Luke's Hospital of Chicago from 1919 through 1955. Fourteen

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appendices were removed by members of the Department of Surgery. Sixteen appendices were removed by members of the Department of Obstetrics and Gynecology. Dr. Edwin F. Hirsch of the Department of Pathology has diagnosed the lesion in each case. It is noteworthy that Dr. Hirsch fixes and sections all appendices coiled after the lumen has been opened longitudinally as illustrated in Fig. 1.

### Preoperative diagnosis

A preoperative diagnosis of endometriosis of the appendix was not made in a single instance. There are no pathognomonic criteria to establish an accurate preoperative diagnosis of endometriosis of the appendix.

Endometriosis of the appendix produced a clinical syndrome simulating acute or recurrent appendicitis in 11 patients. Pathological evidence of inflammatory appendiceal disease was present in 2 of those patients. Endometriosis apparently does not predispose the appendix to infection. Four patients had the initial episode of symptoms or recurrent

episodes of symptoms at the onset of a menstrual flow.

Nausea, emesis, bloating, bizarre generalized abdominal pain, and right lower quadrant or pelvic pain occurring periodically and not related to the menstrual cycle may be caused by endometriosis of the appendix. Physical examination and gastrointestinal studies may not reveal the cause of such symptoms, and such was true in 3 of our patients. Complete subsidence of symptoms followed an elective appendectomy in each patient.

A condition other than appendicitis was diagnosed preoperatively in 19 patients. The appendix was removed electively during the more major surgical procedure in each patient. A clinical diagnosis of pelvic endometriosis was made in 9 of those patients. Endometriosis of the appendix may not produce any symptoms, or, if symptoms due to this lesion do occur, they may be masked by the symptoms of a more major genital disease, or, as in 3 instances, cholecystic disease.

Serious sequelae of endometriosis can oc-

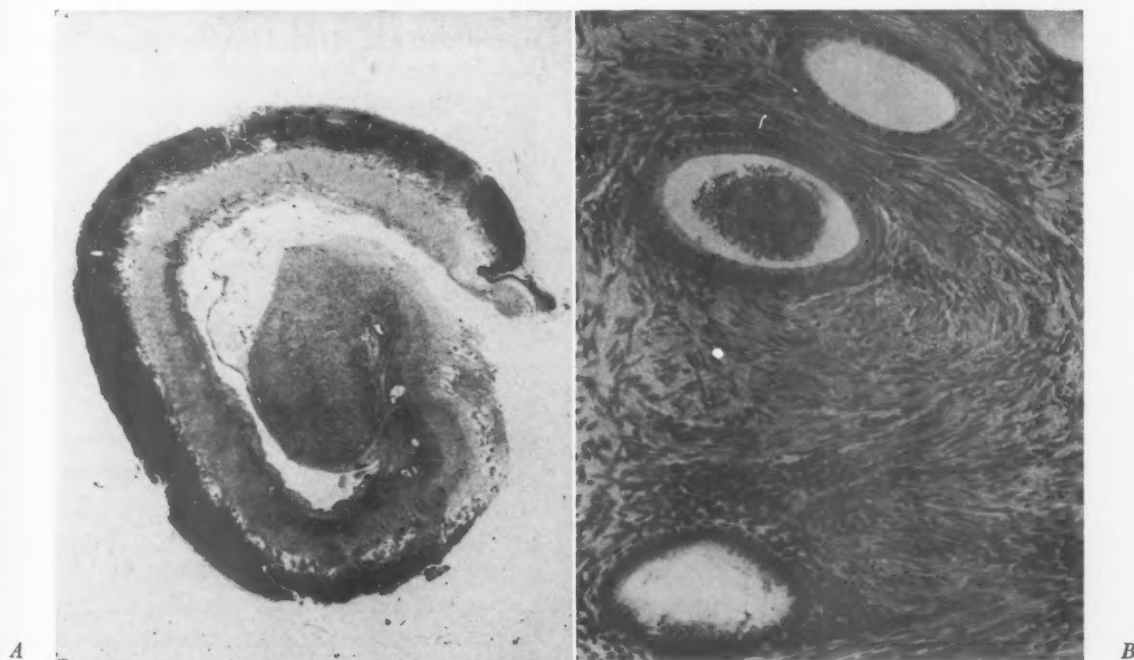


Fig. 1. *A*, The lumen of the vermiform appendix has been opened longitudinally. The appendix is then coiled, fixed, and sectioned. Endometrial glands and a small amount of stroma are noted in the subserosal and muscularis layers near the tip of the appendix. *B*, High-power view illustrating typical endometrial glands and stroma.

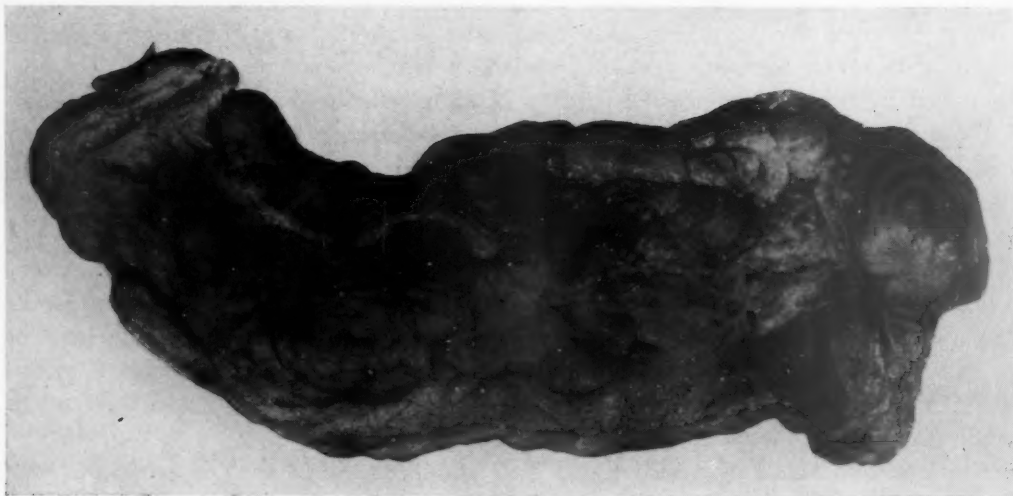


Fig. 2. Photograph of the peritoneal surface of the appendix vermiformis illustrating the hemorrhagic tissues in the retracted scars.

cur. A clinical state completely unrelated to symptoms of appendicitis or of a gynecological disease has been observed. Collins<sup>4</sup> reported a case of severe melena caused by endometriosis in the appendix of a 27-year-old woman. Deacon<sup>17</sup> reported a case of intussusception of the appendix caused by endometriosis. The symptoms of those 2 patients occurred at the onset of a menstrual flow.

#### Operative findings and procedures

Normal pelvic organs were stated to be present during operation in 10 patients who had primary appendectomies performed by general surgeons. A McBurney incision was made in the majority of those patients. I do not believe that one can state with authenticity that pelvic viscera are entirely normal when one is operating through a McBurney incision. The frequent removal of a physiological cyst from the right ovary and practically never from the left ovary supports the doubt that pelvic viscera can be examined adequately through the usual incision for the removal of the appendix. Surely such "cysts" are as common in the left as in the right ovary.

A normal intrauterine pregnancy of 12 weeks' duration was present in one patient. An appendectomy was performed because of

"recurrent appendicitis." That appendix revealed the presence of endometriosis only.

A gross diagnosis of appendiceal endometriosis was made at the operating table in 5 patients. Four of those patients also had extensive pelvic endometriosis. Fig. 2 illustrates the gross appearance of endometriosis of the appendix.

Appendiceal endometriosis was present in a 22-year-old woman who had congenital atresia of the cervical canal associated with an immature corpus uteri and obliteration of the upper vagina.

A routine appendectomy was performed in each of 3 patients who underwent a cholecystectomy for chronic cholecystitis and cholelithiasis. A complete hysterectomy and bilateral salpingo-oophorectomy had previously been performed for pelvic endometriosis in one. There was no gross evidence of residual pelvic endometriosis in that patient. The pelvic organs were described as normal in the operative record of one patient and there was no descriptive note of the pelvic organs in the record of the third patient.

Sixteen patients had partial or total removal of their reproductive organs, together with an elective appendectomy. There was gross evidence of appendiceal endometriosis in 4. Those 4 patients also had gross pelvic endometriosis.



A most interesting finding was the absence of endometriosis in the right ovaries of 3 patients. This finding does not coincide with Sampson's<sup>18</sup> observations which prompted his idea that the ovary normally acts as "a sort of intermediary host, hot-bed or incubator" and that "the intestinal growth follows rupture of the ovarian hematoma with liberation of its endometrial lining into the peritoneal cavity." Sampson's 4 cases of appendiceal endometriosis were associated with "ovarian hematoma" in the right ovary only. Senapati<sup>7</sup> states that right ovarian endometriosis is present in all cases of appendiceal endometriosis. We cannot concur in such a conclusion since 3 patients in our series had no pathological evidence of endometriosis in the right ovary.

### Histopathology

The mucosa of the appendix was not involved by endometriosis in any of the cases. This finding is consistent with the fact that mucosal involvement with endometriosis in other portions of the bowel or bladder occurs most rarely. A pertinent observation also is that bleeding into the areas of endometriosis was found in only one appendix. Perhaps the infrequent finding of mucosal involvement of the appendix and the rare occurrence of hemorrhage into the endometriosis account for the absence of secondary inflammatory findings as noted in all the appendices in this series except 2.

The subserosa of the appendix was the most frequent location of endometriosis. There was no relationship between the histological location of the endometriosis in the appendix and the clinical syndrome presented by the patient. Certainly this was true in the 11 patients with a preoperative diagnosis of appendicitis. It is presumed that endometriosis in the appendix caused the symptoms and physical findings which led to operation in the latter patients, with the exception of 2 patients who had inflammatory findings associated with the endometriosis in the appendix. Sutton and Hardy<sup>5</sup> raised the question of whether or not involvement of the muscular layer of the ap-

pendix with endometriosis may be the determining factor for the presence or absence of symptoms comparable to those of acute appendicitis. The findings in the present study do not offer support for this contention. The mechanism whereby endometriosis in an appendix may produce symptoms simulating appendicitis is unrelated to the histological location of the endometriosis in the majority of the cases. On the other hand, it may be that hemorrhage into endometriosis or associated infection may better explain the presence or absence of symptoms. However, such pathological findings were strikingly absent in the majority of our cases.

Pregnancy was diagnosed from the histological study of one appendix. An appendectomy was performed on a 34-year-old woman who was 12 weeks pregnant. The pathologist, without benefit of prior knowledge that the patient was pregnant, made a diagnosis of pregnancy from the marked decidual reaction of the endometriosis in the subserosal and muscularis layers of the appendix.

### Summary

1. There is no clinical syndrome pathognomonic of endometriosis in the appendix. A presumptive diagnosis of this lesion may be entertained in selected cases of right lower quadrant pain in the sexually mature woman.

2. Acute or recurrent appendicitis was the preoperative diagnosis in 11 patients in this series. Primary appendectomies were performed in all patients, but gross evidence of appendiceal endometriosis was recognized at the operating table in only one.

3. Appendiceal endometriosis apparently does not predispose the appendix to infection since inflammatory findings were present microscopically in only 2 instances.

4. A disease other than appendicitis was diagnosed preoperatively in 19 patients. A gynecological problem was the indication for laparotomy in 16 patients and cholecystitis in 3 others.

5. Right ovarian endometriosis was not present pathologically in 3 patients, which does not conform with the conclusion of

Senapati<sup>7</sup> that right ovarian endometriosis always accompanies appendiceal endometriosis.

6. The subserosal layer of the appendix was the most frequent histological location

of endometriosis. No relationship was established between the histological location of endometriosis in the appendix and the clinical state of the patient.

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#### Discussion

DR. GEORGE H. GARDNER, Chicago, Illinois. Obviously, involvement of the appendix by endometriosis occurs infrequently. Although this lesion was first brought into focus by Sampson in 1921, only 200 instances have thus far been reported, including the 30 in Dr. Lane's series. Furthermore we have been told that Collins found only 54 in a study of 100,000 appendices—a frequency of 0.054 per cent. On the other hand, Dr. Lane cited 4 other articles which, together, reported 11 instances of appendiceal involvement in 2,140 cases of pelvic endometriosis—a frequency of 0.54 per cent, or exactly 10 times oftener than in Collins' experience. However, this composite of patients with pelvic endometriosis originated from 4 different medical centers, and there is a striking variation in the frequency of appendiceal endometriosis in those 4 reports; actually, it ranges from 1.35 per cent down to 0.176 per cent—in other words, from one case in 76 to one in 569. Such amazing differences in frequency immediately suggest 2 contributing factors over and beyond the well-recognized fact that any and every lesion turns up most frequently when one is constantly on the alert for it. Here, however, one wonders, first, if appendices were removed routinely from each of those 2,140 patients with pelvic endometriosis. Second, it is almost redundant to comment on the striking discrepancy

between the number of gross lesions of endometriosis in the operating room and the number so diagnosed microscopically by the pathologist in the laboratory.

Nowadays there can be little justification, except prejudice, for a gynecologist's unwillingness, almost as a routine, either to explore the abdomen or to remove the appendix. Such routine appendectomies require only a few minutes, do not jeopardize the patient's convalescence, and do not increase the frequency of postoperative morbidity. Granted that the majority of such routinely removed appendices are normal; yet, there is a surprising frequency of those which are abnormal in one way or another. In my own experience, such previously unsuspected disease in the appendix has included not only endometriosis but also chronic appendicitis, acute suppurative appendicitis, mucocoele, carcinoids, and even an implant of carcinoma of the endometrium once when I had inadvertently perforated the uterus 5 days earlier at the start of a curettage. In addition to the occasional fortuitous removal of such a variety of disease processes, one should not willfully deprive patients of the prophylactic value of such routine appendectomies.

Further, regarding the marked discrepancy between the frequency of gross endometriosis, whether or not it is recognized at the operating table, and that which is so diagnosed micro-

scopically by the pathologist, one must grant that there are distinct advantages to the method employed by Dr. Edwin F. Hirsch, St. Luke's eminent pathologist. He fixes and sections all appendices, coiled like an anchovy, after the lumen has been opened longitudinally; such technique should be expected to yield a higher percentage of accurate diagnoses. On the other hand, if pathologists do not cut blocks from fresh tissues, they may not recognize endometriotic lesions, as they will have lost much if not all of their characteristic color; hence blocks may not include involved areas. Furthermore even in those sections which include lesions, one frequently fails to find the classical microscopic criteria for a diagnosis, namely, the combination of typical glands and stroma, and most pathologists are extremely reluctant to diagnose endometriosis except in the presence of such classical microscopic criteria.

Also, we should not be surprised that appendiceal endometriosis is essentially a "silent" lesion, i.e., a chance finding and one that does not arouse clinical suspicion of a diseased appendix except on rare occasions. Such lack of symptoms coincides with our own clinical experience with so many instances of pelvic endometriosis. A large number of these, so diagnosed clinically, on the basis of typical beading lesions in the uterosacral ligaments and/or rectovaginal septum, are totally asymptomatic; they need only to be watched, and few, indeed, have shown evidence of progressive development dur-

ing the years that they have been observed. Others are chance findings at laparotomy performed for some other condition and, in retrospect, one can only conclude that they, too, were "quiet," had not caused symptoms, and in no way were responsible for the patient's need for operation.

DR. EUGENE A. EDWARDS, Chicago, Illinois. Only 5 of the patients in this series had a sufficient number of endometrial nodules in the appendix to permit a diagnosis of appendiceal endometriosis at the time of operation. Grossly, these lesions may be located at almost any area in the appendix. They are hard, nodular, and puckered. A carcinoid of the appendix must be considered and differentiated from an endometrial lesion. A carcinoid in the appendix is almost invariably located at the tip of the appendix. It, also, is nodular but is smooth rather than puckered. A carcinoid, to my knowledge, is the only lesion in the appendix which may simulate endometriosis.

Fourteen patients in this series, with pathological diagnoses of endometriosis of the appendix, were operated upon by general surgeons using the McBurney incision. Clinically, 10 of these cases showed no pelvic endometriosis. Had the abdomen been opened by a midline incision and a careful exploration of the pelvic organs been made, we believe that the endometrial nodules would probably have been discovered in a majority of the cases.

# Giant histologic sectioning of entire uterus

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IN THE course of studying pathologic anatomic changes, it is sometimes desirable to demonstrate entire lesions with associated changes in the surrounding tissues such as metastases, irradiation effects, and so forth. This amounts to a consideration of anatomical relations in a magnitude between microscopic and macroscopic dimensions but including both. In addition, by serially sectioning, the third dimension of an organ or lesion can be appreciated so that accurate quantitative representation of any given pathologic change is obtained. This ideal analysis of organs or lesions has been perfected by neuropathologists in sectioning whole brains.<sup>1, 2</sup> There has been limited application with use of blocks cut to fit lantern slide sized glass in studying cancer of the stomach,<sup>3</sup> bronchus,<sup>4</sup> and cervix<sup>5</sup> by Gall and co-workers. There are excellent studies in the recent past on routine sized blocks of cervix with carcinoma in situ.<sup>6, 7</sup> All of these studies, however, are based on paraffin-embedded material which limits the practical size of the sections to a few square centimeters.

The method presented here is a celloidin embedding technique almost identical with that used more than three decades ago by Dr. J. A. Sampson in developing his controversial theory regarding the implantation

histogenic theory of endometriosis. It is believed that while the technique is suited to studying organs involved in heart disease, tuberculosis, arthritis, and nephritis, it is uniquely adapted to the study of gynecologic cancer, irradiation lesions, human embryology, and prematurely separated or abnormal placentas.

This is a report of work directed toward facilitating and simplifying the technique so that its application can be extended.

## Materials and methods

A giant sliding microtome as used in cutting whole brains is satisfactory (Fig. 1). This was perfected by the Mico Instrument Co., Cambridge, Massachusetts. Also the large microtome made in Germany by the Sartorius Co. is adapted to this size of specimen. The mounting stages measure 24.5 by 14.0 cm. and will accommodate blocks of tissue varying from 1.0 to 10.0 cm. in thickness.

Honing, stropping, and maintenance of a steel cutting knife of such large dimensions is no longer practical by the ordinary laboratory personnel. A better cutting edge is maintained by use of a 75.0 cm. replaceable razor blade strip\* which is screwed down to a rigid blade holder which the manufacturer furnishes. This is a recent improvement over the knife shown in Fig. 1. The disposable blade insures good cutting edges replaced at an average cost of 60 cents per blade. This precision-machined instrument

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\*Obtainable from the Gillette Safety Razor Co., Boston, Massachusetts.



enables the average operator to cut consistent serial sections of well-embedded celloidin material at 15 to 20  $\mu$ .

Pilot work utilized the whole hysterectomy specimen (Wertheim type) (Fig. 2) and also block resected pelvic viscera from the "exenteration" or Brunschwig type operations performed for uterine cancer (Fig. 4). For this use it is desirable that the specimen remain as nearly intact as possible, without preliminary cutting or taking of many routine, small blocks. If trimming of a tissue specimen is essential for immediate diagnosis, one or more small blocks can be taken without destroying the visceral or lesion relations. When a uterus has been previously opened, it is possible to partially reconstruct the specimen by suturing with continuous black silk sutures on curved cutting edge needles, approximating the appropriate cut surfaces.

Fixation, dehydration, and celloidin embedding of these large whole specimens take from 6 to 9 months. If speed of diagnosis or reporting is important, however, the process can be shortened by increasing the temperatures 5 to 10 degrees above room temperature with use of a semivacuum embedding system or by sectioning the whole specimen, after fixation, into several 2.0 to 3.0 cm. thick serial "slabs" which will remain flat throughout the dehydrating series of alcohols. For example, Fig. 2 shows a specimen consisting of uterus, tubes, and ovaries, together with paracervical and paravaginal tissues "blocked" or cut in a frontal plane into "slabs," ready for embedding in celloidin. This blocking shortens the time necessary to pass through the dehydrating and embedding series about 50 per cent.

These blocks can be oriented successfully by India ink markings on opposite surfaces. It is necessary to plan the cutting at this stage so as to show desired relations of any given tumor or abnormality. For example, if it is desired to show spread of metastatic disease to the parametrium and lateral walls of the uterus, frontal sectioning is best suited; if irradiation changes in



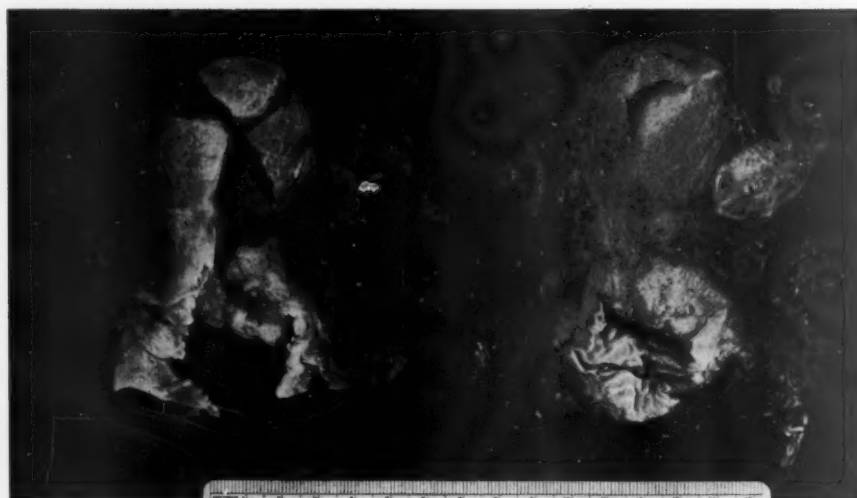
Fig. 1. Giant microtome used for serial celloidin sectioning of whole viscera, showing 75.0 cm. blade with adjustable angle and mounting stage, 24.5 by 14.0 cm., lowered by precision gear to accommodate block 10.0 cm. in thickness.

the base of the bladder or the rectum are to be studied, sagittal sectioning is planned. This type of preliminary blocking is also illustrated in Fig. 4, which shows an "exenteration" type specimen of pelvic cancer resected en bloc for cervical cancer. Obviously, prefixation cutting or blocking is undesirable if very accurate information is required as to the relations or measurements of the lesion.

Dehydration is accomplished by the usual manner of passing the specimen through a graded series of alcohols—two changes of 80, 85, 90, 95, and 100 per cent alcohol. Changes thus made every 2 weeks are usually sufficient to dehydrate an average specimen such as a uterus. Following the final alcohol, the specimen is placed in a mixture of 50 per cent absolute alcohol and 50 per cent ether, and the jar is sealed with adhesive tape and left to stand for a day or more. At this point, dehydration is usually complete.

Embedding is done best by the manner described in the standard reference books of histology technique (Mallory, Lillie, or McClung). Parlodion\* is the best choice of nitrocellulose for the purpose. The uterine

\*Mallinckrodt Chemical Works' trade name for purified pyroxylin.



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**Fig. 2.** Gross view of Wertheim hysterectomy specimen cut into two frontal "slabs" for embedding and sectioning. *Left*, anterior "slab"; *right*, posterior "slab."

**Fig. 3.** Two levels from histologic serial sections 25  $\mu$  in thickness cut through entire uterus, vagina, Fallopian tubes, and ovaries of blocks shown in Fig. 2.

specimens stay from one to 2 weeks in 4 per cent celloidin, 2 to 4 weeks in 8 per cent, and 2 to 4 weeks in 12 per cent. A longer time is needed for the larger specimen or multiple viscera. Chloroform poured on 12 per cent celloidin and left overnight will render the block sufficiently hard so that it can be cut with the microtome the following day. The block can be stored indefinitely in 80 per cent alcohol.

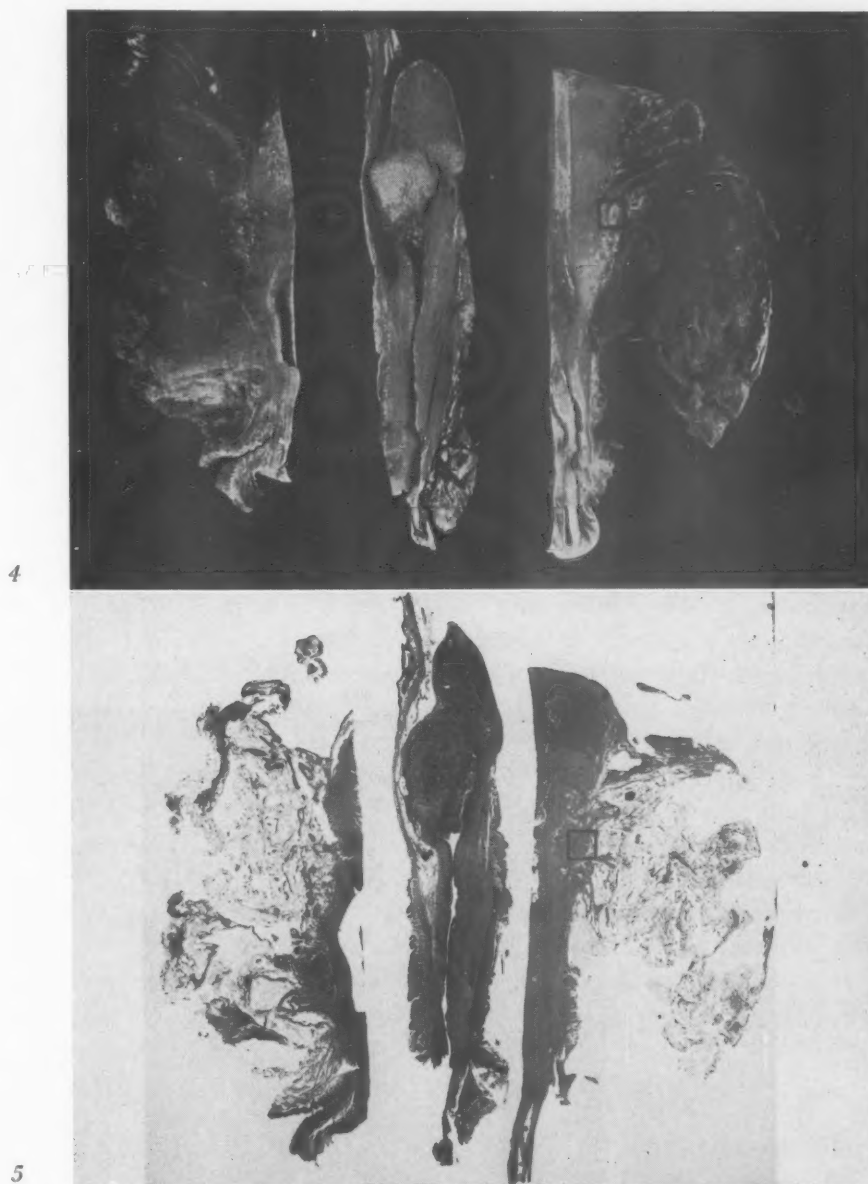
When the blocked and embedded tissue is to be cut, the following procedures should be observed: (a) the hardened block should be placed on the mounting plate and

trimmed so as to have a small margin of clear celloidin around the tissue block; it should also be level so that the plane of the desired cut will be attained; (b) mounting should be accomplished by pouring 12 per cent on the mounting stage and placing the block on the celloidin in the desired position; (c) the block and stage should be immersed in a pan of 80 per cent alcohol and/or chloroform to cause it to harden within 8 hours. It is necessary to keep the celloidin block moist with 80 per cent alcohol at all times.

In cutting, consecutive sections are taken

off serially on toilet tissue paper; that is, by laying tissue squares wet with 80 per cent alcohol over the block with each cut so that the thin celloidin section is picked up with the tissue paper. Every tenth or

twentieth section is stained routinely, giving representative levels throughout the block at fixed intervals. The distance between these intervals is the product of the thickness of the sections times the num-



**Fig. 4.** Gross specimen of exenteration operation for Stage III cancer of the cervix. *Left*, right lateral portion of specimen containing right ureter, internal hypogastric vessels and lymphatics, right tube and ovary, and lateral portion of uterus. *Middle*, mid-sagittal "slab" containing uterus and cervix with tumor, base of bladder, urethra, attached (opened) rectosigmoid, anus, and associated supporting structures. *Right*, left lateral portion of specimen containing corresponding structures.

**Fig. 5.** Photograph of histologic sections cut at 25  $\mu$  through whole blocks of pelvic viscera illustrated in Fig. 4, showing cervical tumor mass encroaching on rectal wall, base of bladder including urethra at mid-sagittal level, and ureter with tumor infiltration in left lateral block (box).



Fig. 6. Photomicrograph prepared from histologic section in boxed area, Fig. 5, showing left ureter in cross section with tumor metastases. ( $\times 16$ ; reduced  $\frac{1}{4}$ .)

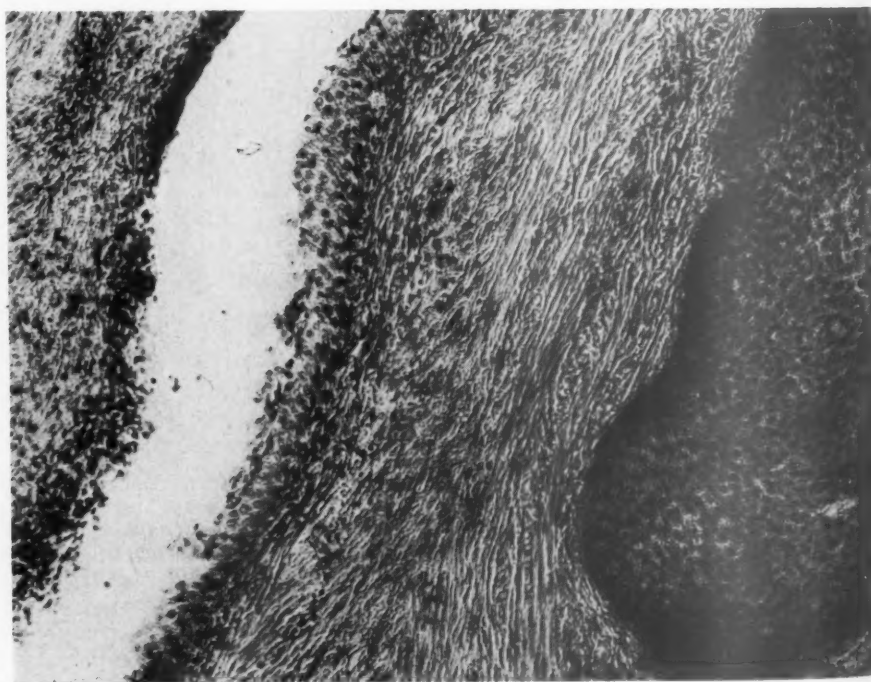


Fig. 7. Photomicrograph prepared from histologic section in Fig. 5 showing higher power of ureter and tumor island represented in preceding photograph. Note mitotic figures in right lower field. ( $\times 250$ ; reduced  $\frac{1}{4}$ .)



ber of sections between the representative stained levels. The remainder of the sections can be stacked with interval numberings as to levels and stored in 80 per cent alcohol until needed, or indefinitely.

At present, the entire process, from start of dehydration to the permanent mounting, takes from 6 to 12 weeks for uteri and up to 8 months for "exenteration" type specimens.

Staining is done in 5 by 7 inch Pyrex baking dishes. These are large enough to hold the largest section that can be cut from the 24.0 by 14.0 cm. stage. We have used all types of stains with excellent results. Care must be taken to avoid over-staining due to the large size and thickness of the sections. Higher alcohols have a tendency to dissolve the celloidin gradually, and aqueous counterstains are used whenever possible.

The stained celloidin sections can be cleared with Terpeneol, trimmed of excess celloidin edges, and mounted with Permount. Ordinary picture glass measuring  $\frac{1}{16}$  inch in thickness is used. It is cut in 5 by 7 inch rectangles to accommodate these large sections. A second piece of picture glass, measuring  $\frac{1}{4}$  to  $\frac{1}{2}$  inch smaller in size, is used for a cover glass. The mounts are stacked between small squares of Masonite or plywood in groups of 8 to 10 with 1,000 or 2,000 Gm. counterweights and allowed to dry for a week to 10 days. The mounts are useful as "hand" demonstrations for students or clinicians when viewed grossly with adequate light from an x-ray view box, window, or other light source. In this use, they have been found extremely durable and exhibit the same features as laminated Duraglas when accidentally dropped. By use of any type of hand lens, structural abnormalities and visceral relations can be studied (Figs. 3 and 5). In microscopic study it may be necessary to reverse the slide from left to right on the stage in order to cover the entire microscopic field because the size of the mount exceeds the depth of the usual microscopic stage. It has been found that mag-

nifications over  $\times 300$  are impracticable and the usual combinations of  $\times 5$  to  $\times 15$  eyepieces with 30 mm., 16 mm., or 8 mm. objectives on an ordinary binocular microscope yield good visualization of such details as mitotic figures, tumor emboli in lymphatics, radiolytic effects, and so forth (Figs. 6 and 7).

#### Comment

Fixation and embedding of an entire specimen *in toto* with subsequent serial sectioning is best suited to topographical studies of small lesions in which it is desired to make three-dimensional reconstructions in order to study the pathologic anatomy such as has been done by Foote and Stewart<sup>6</sup> and more recently by Przybora and Plutowa.<sup>7</sup> Dividing the fixed or unfixed specimen into smaller "slabs" or blocks and subsequent serial sectioning actually are more complicated, tend to render the final product a sampling of intermittent levels of the lesion, and are subject to great inaccuracies. The multiple block technique tends to increase artifactual shrinkage and warping due to fixation and dehydration. This in turn jeopardizes accurate mensurative observations and largely invalidates statistical analyses based on them.

It can be appreciated readily that only by fixation of the entire specimen intact and by serially sectioning can the material be completely studied for metastatic lymphatic spread of tumor, tumor emboli, and associated metaplasia, inflammation or visceral change, or, most important, multiple foci of disease.<sup>8, 9</sup>

#### Summary

A relatively simple celloidin embedding technique is presented which, when used with a giant sliding microtome such as illustrated, produces giant histologic preparations averaging 25  $\mu$  in thickness, and which are suitable both for gross demonstration or study of whole cancers or viscera and for microscopic magnifications of  $\times 50$  to  $\times 300$ . The cost of preparing such a specimen ranges from \$20 to \$30 per case exclusive

of technical help. The technique is thought particularly applicable to analysis of cancerous growths and treatment effects.

This technique was made possible by the kindly advice and help of Dr. Paul I. Yakovlev, Clinical Professor of Neuropathology, Harvard

Medical School.

Portions of the surgical material in this report were derived from the Laboratory of the Chelsea Naval Hospital and Massachusetts Memorial Hospital, Dr. S. C. Sommers, pathologist, and Dr. L. Parsons, surgeon.

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# TMK-101, "Türk," a new rapid polychrome staining technique for office practice

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IN AN effort to supplement staining techniques now employed in cytodagnosis, we present a new dye especially suitable for use in the physician's office. This method is simple, inexpensive, and rapid, and it gives adequate indication of impending difficulties for the patient.

## Method

A mixture or combination of 2 dyes was compounded to produce a stain which is called TMK-101 or "Türk."

TMK-101 or "Türk" (T-M-K-10-1) represents:

T: Without fixation.

M: Represents blue dye, *Sheaffer Pen Company's No. 232 Permanent Blue-Black Ink* (produced with C.I. No. 707 and/or 671).

K: Represents red dye, *Sheaffer Pen Company's No. 032 Permanent Red Ink* (produced with C.I. No. 179, 768 and/or diphenyl; *fast Light Red 6 BF, Geigy Company*).

101: Indicates the ratio of 10 M to 1 K.

## Preparation of TMK-101 4 per cent solution

### 1. Undiluted TMK-101 (100%)

In a dark bottle (55 c.c.) mix

50 c.c. M (approximately 20 drops equal 1 c.c.)

5 c.c. K (approximately 20 drops equal 1 c.c.)

*From the Cancer Institute at Miami, Cancer Research and Cytology Center*

*Presented as a scientific exhibit at the annual meeting of the Florida Medical Association, Bal Harbour, Florida, May 2-6, 1959.*

A small crystal of phenol may be added to prevent deterioration.

### 2. Diluted 4 per cent solution

a. 24 c.c. distilled water in a staining jar

add 1 c.c. above undiluted TMK-101, shake, or use inks direct:

b. 25 c.c. distilled water

add 20 drops M (blue ink)

add 2 drops K (red ink).

Shake gently

**Note.** Latter preparation (2, b) is preferable for individual cases.

**Instrumentation.** The cervix is examined through a bivalve speculum. The Ayre wooden spatula is inserted through the vaginal speculum and applied to the cervical surface, then turned completely around. Very little pressure is exerted.

The area of the squamocolumnar junction is extremely important since most cervical cancer originates at this site.<sup>1, 3, 4</sup> The Ayre spatula is the best tool for collecting material, if a perfect smear is to be made.

After the material is obtained, the tip of the spatula containing the secretion is applied to a clean, dry, glass slide, and smeared carefully. For the best smear to be obtained, the spatula must move parallel to the glass slide. One rapid movement is sufficient.

The smear material must be spread in a very thin layer. Before drying and without fixation, the slide is immediately and gently placed in a staining jar containing 4 per cent solution of TMK-101 in distilled water. After 15 minutes in this solution (at room temperature), staining of the slide is com-

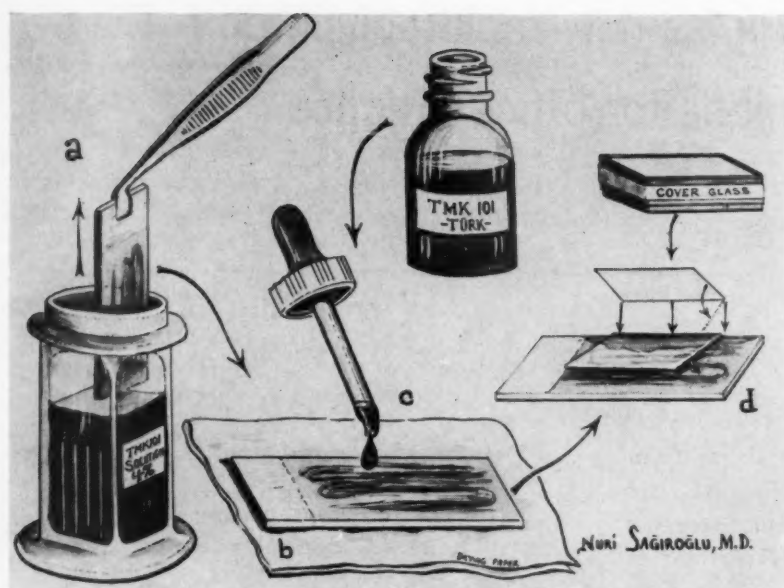


Fig. 1. *a*, Slide is removed from staining jar after 15 minutes or longer; *b*, it is placed on a drying filter paper; *c*, one or two drops of the same TMK-101 solution is added on the smeared side as mounting medium; *d*, a clean cover slip is placed on top and the specimen slide is now ready for microscopic examination.

plete. This is believed to be the minimal period of time the physician may require for performing other physical examinations. While the patient is dressing, the physician can mount the slide and examine it under the microscope.

**Mounting.** The slide is removed from staining solution after 15 or more minutes and placed on dry filter paper, smeared side up. The mounting medium consists of 3 or 4 drops of the same dye solution. A clean cover-slip is placed on the surface of the smear. To prevent air bubbles, the specimen is covered as shown in Fig. 1.

As the first step in mounting, the cover slip is touched parallel to one long edge of the smeared place at the narrow angle. The mounting medium is collected in that angle. The angle is narrowed by moving the cover slip and, finally, the area is completely covered. The excess staining solution overflowing the edges is absorbed by dry filter paper. The bottom and edges of the slide are wiped carefully before examination.

**Microscopic examination.** The slide is examined immediately after mounting. If the mounted slide is allowed to stand for more than 15 minutes before microscopic exami-

nation, the mounting medium will evaporate and the slide will become dry. In this condition, it is not suitable and will be of no value for diagnostic purposes. However, the edges of the cover slip may be sealed by smearing with colorless nail polish; or, the slide may be preserved simply by replacing it in the same dye solution. The slide, in solution, may be preserved for a few hours, a few days, or longer if desired. Thus preserved, the slide will retain its diagnostic value and there will be no overstaining.

**The pipette method.** The pipette used in these studies was attached at one end to a strong rubber bulb with a large opening at the opposite end. It is advisable to obtain the material from the squamocolumnar junction. This is done by moving the mouth of the pipette along the squamocolumnar circle of large and eroded cervixes with frequent aspiration. Material obtained with the pipette is dropped onto the middle of the glass slide. A possible alternative technique is to prepare a solution of the material aspirated by washing the pipette with 2 to 3 c.c. of normal saline in a glass tube. A drop of the latter is applied to the surface of a glass slide and 1 drop of TMK-101, un-



diluted, is added. With the use of a bacteriologic wire loop, the 2 solutions are mixed, without spreading. For mounting, the cover slip is placed on the mixture as described for the spatula method.

The staining is instantaneous with the pipette method. It is possible to prepare a mounted slide in exactly one minute. This method can be the most rapid yet developed

for cytologic staining. With this method, cellular diagnosis can be completed in 5 minutes.

**Brush technique.** In this method, a specifically designed soft brush is applied to the lesion to obtain material. The smear is prepared and stained as described for the spatula method.

Cotton swabs may also be used to obtain

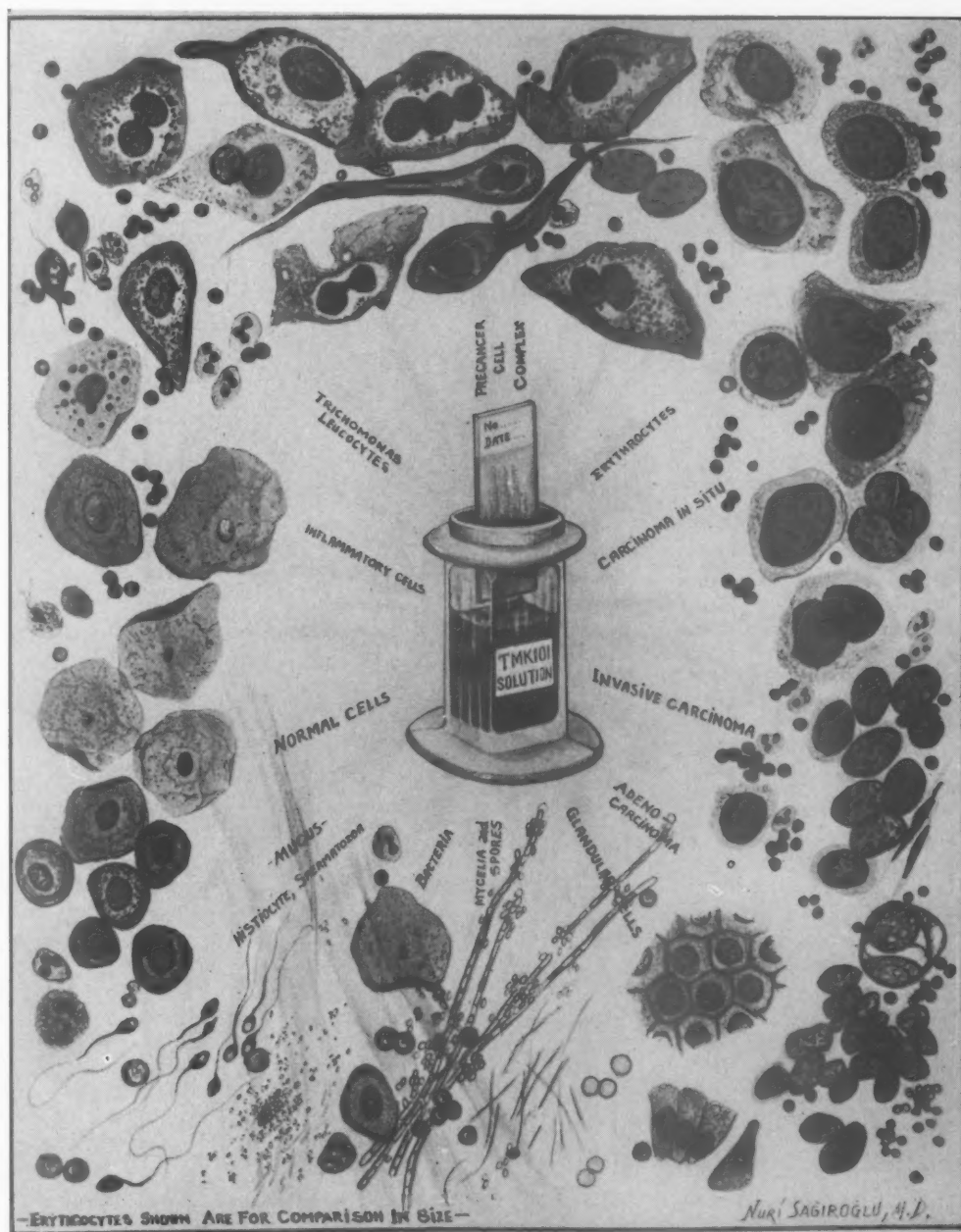


Fig. 2. The cells and microorganisms in the smear stained by TMK-101 under microscope.

material. The smear technique, in this instance, is the same as that used in the spatula method. After the lesion is swabbed, the cotton swab is rolled on the slide from one end to the other.

Pipette brushes and swabs serve moderately well, but they are not as efficient as the spatula.

### Material

A majority of the smears stained by the TMK-101 method were obtained from 315 research patients of the Cancer Institute at Miami who received monthly checkups for varying periods of time (Table I). The TMK-101 staining technique has been used more than 5,000 times since February, 1957,

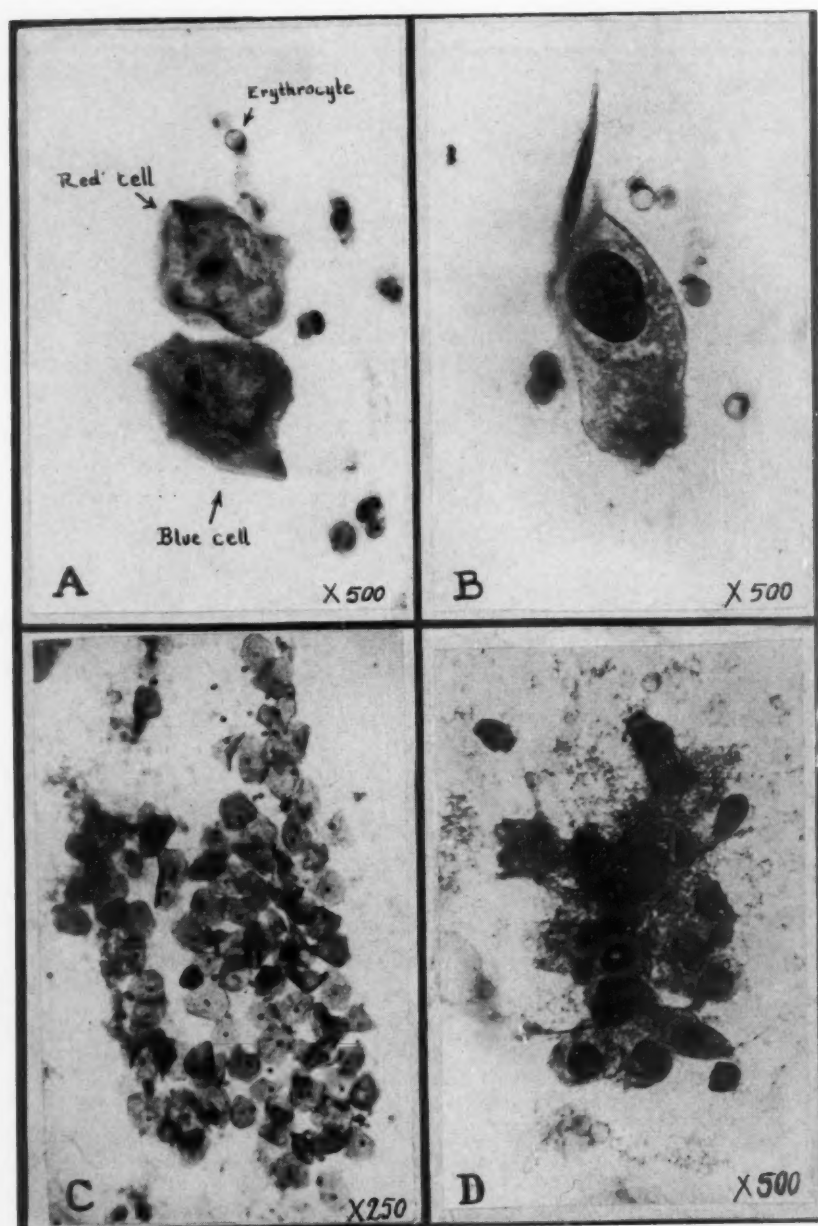


Fig. 3. Photomicrographs from smears stained with TMK-101. A, Two normal cells with erythrocyte and leukocytes. B, Malignant cells from in situ carcinoma; compare the nuclear sizes and chromatin content in A and B. C, A cell cluster in a normal smear. D, Cell cluster, preinvasive cervical squamous cell carcinoma (cancer in situ).

to stain the smears of material taken from these patients. In all cases, smears were also prepared by means of the Papanicolaou method which is the staining technique routinely employed in our institute for diagnostic purposes. Diagnostic results were almost identical.

### Results

TMK-101 mixture has a great staining capacity (Fig. 2). All types of cells and

microorganisms in the smears, as well as those direct from biopsy tissue<sup>5</sup> and urine sediments,<sup>10</sup> are stained without preliminary fixation.

### Cellular components

**Cytoplasm.** A variety of color ranging from carmine red to dark violet is assumed by the cytoplasm. With TMK-101, the cornified cell, under normal conditions, takes red dye the same as when the Papanicolaou

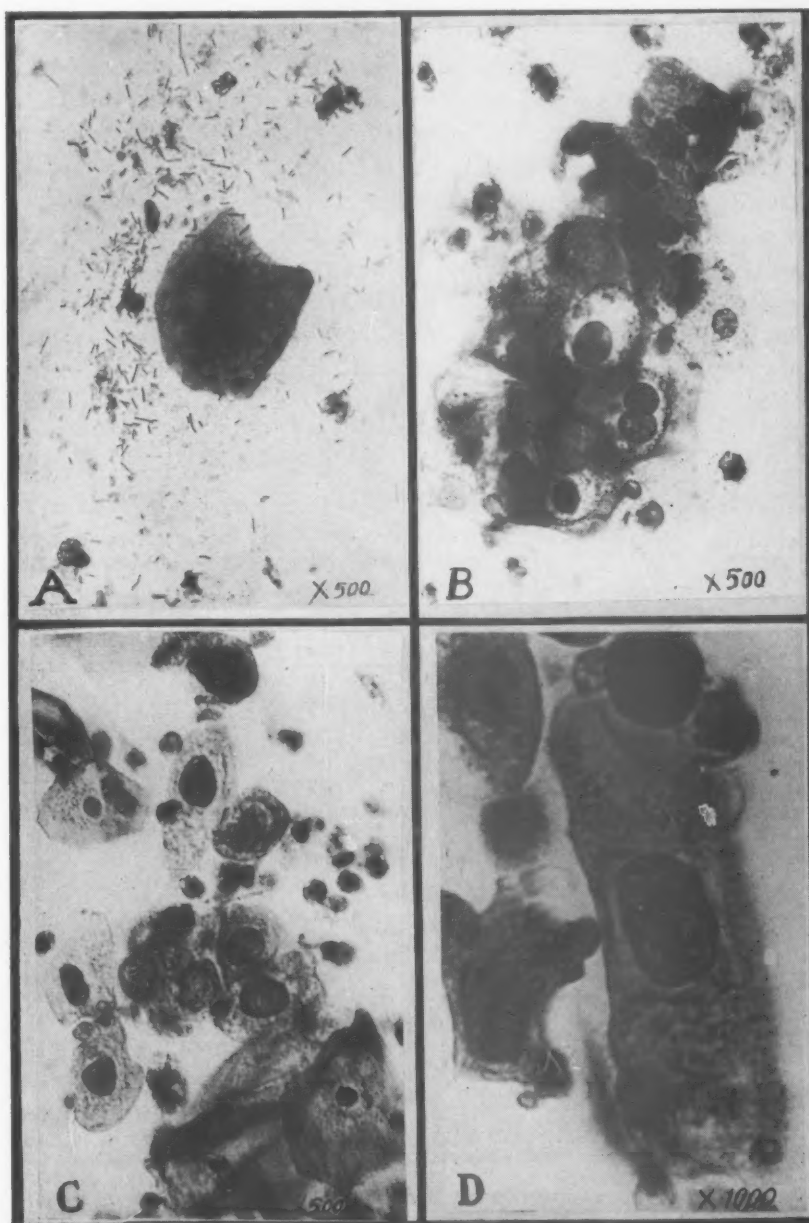


Fig. 4. *A*, A normal cell and Döderlein bacillus in pregnancy. *B*, Precancer cell complex or dyskaryotic cells. *C* and *D*, Malignant cells, cervical carcinoma.

method is used. In some other conditions (inflammatory, precancer, and cancer), the inactive or dead cells probably stain red.

The deeper layer cells usually stain some shade of blue; however, they may stain violet which is evidence that such darker colored cells are neutrophilic.

All cellular details are sharp and distinct. If the cytoplasm has globules, these stain the same color as the cells, but the coloration is much more intense, and they are "shiny" and homogenous. The cytoplasm of the glandular cells stains light blue-violet.

**Nuclei.** Although the nuclei stain the same basic color as the cytoplasm, the color tone is much darker. The nuclear membrane and the chromatin stain the darkest (Fig. 3). The nucleoli stain sharply and are the darkest part of the nuclei. Where inflammatory conditions are present, the nuclei are enlarged and appear fuzzy and dull. The color tone is almost the same as that displayed by the cytoplasm. The chromatin material and nuclear membranes are fuzzy. Clear chro-

matin content in the nuclei cannot be seen except in the nucleoli. It is the most prominent part of inflamed nuclei.

**Anaplastic cells (precancer or dyskaryotic cells).** The anaplastic cells appearing in smears immersed in TMK-101 solution stain as follows: The nuclei are large and darker than normal, usually showing either dumbbell shape or multinucleation (Figs. 4, B; 5, B and C; 6, A, B, C, E, F, and G). At times, a large halo (paranuclear halo) is observed around the nuclei<sup>6-8</sup> (Figs. 5, B; 6, C, E, and F).

**Leukocytes.** The cellular membrane always assumes intense coloration in the leukocytes. The cytoplasm is extremely light and foamy and usually shows some granulation. Polymorphous nuclei stain a dark color. The acidophilic, basophilic, and neutrophilic leukocytes also pick up TMK-101 stain (Fig. 2).

**Erythrocytes.** The cellular membrane is stained a very dark red, or, sometimes, brown; the cytoplasm is pink and homogenous. Frequently, a polar body (probably Corps of Jolly or degenerated hemoglobin) will be seen eccentrically in the erythrocytes. Such bodies stain dark blue (Figs. 2; 3, A and B).

**Histiocytes.** The histiocytes are easily observed and usually show eccentric nuclei in their foamy, lightly stained, shapeless cytoplasm.

**Spermatozoa.** Spermatozoa stain slowly. The outline of the cells and tails stain dark blue inside a tiny red border.

**Trichomonas.** The protozoic trichomonad stains bluish violet, rarely red. It is possible to observe such bodies, tails, and flagella stained all the same color. The nuclei absorb only a small quantity of stain and are lens-shaped. The cytoplasm usually shows granulation and stains red. *Trichomonas vaginalis* generally have a spherical shape in stained smears (Figs. 2 and 6 H). Occasionally, however, pear-shaped flagellates are observed.

**Mycelia.** Complete with spores, the mycelia look something like a plum tree laden with blossoms. All mycelia and spores

**Table I.** Application of TMK-101 staining technique on specimens obtained from 315 patients and findings

<i>Cervical scraping smears*</i>	<i>No. of cases</i>
Normal, Grade 0	15
Inflammatory (Grade I, A)	65
Precancer (Grades I, B, II, A and II, B)	148
Cancer (Grades III, A, III, B and III, C)	44
Other:	43
Mouth, inflammatory	4
Throat, suspected cancer	1
Inflammatory	4
Lip, inflammatory	5
Stomach (brush), inflammatory	3
Face, skin lesions (3 of these were epithelial cancer, 1 inflammatory)	9
Endometrium (by brush), cancer	1
Inflammatory	7
Scalp, epithelial cancer	3
Inflammatory	1
Breast secretion:	
Adenocarcinoma	1
Inflammatory	4

\*In addition, breast smears were obtained from 75 of the patients and stained in TMK-101. One case was diagnosed as adenocarcinoma; the others were inflammatory or normal.

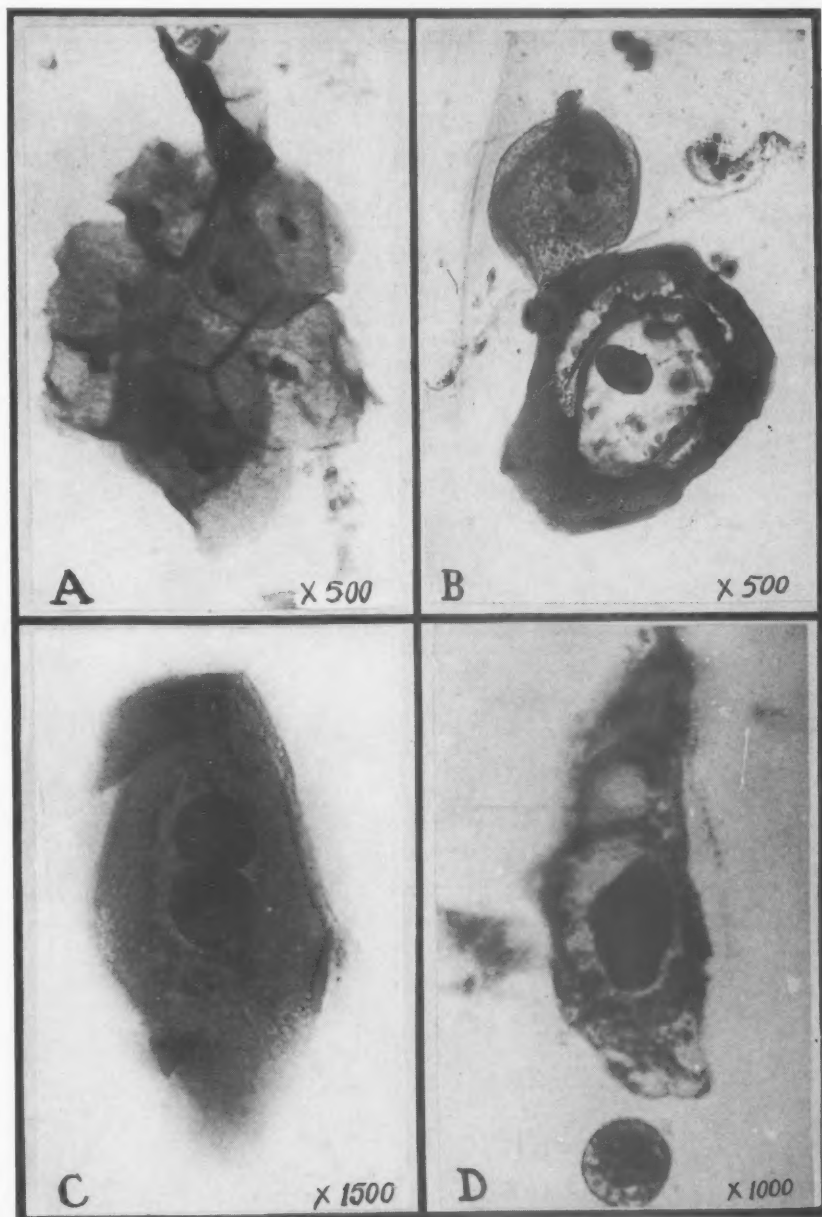


accept TMK-101 stains. The spores stain blue and/or red, and they display slight waving movements. The mycelia are seen frequently en masse, with variegated coloration. They continue to grow in the mounted slide (Fig. 2).

**Background.** Produced with 4 per cent TMK-101 solution as mounting medium,

the background is clear, azure blue. The cells readily absorb all of the stain and, thus, the background remains clear and clean.

**In pregnancy.** The smear stained with TMK-101 shows all the characteristic cellular features of pregnancy. The cells are "thick" and thus stain darker; from 10 to 25 per cent stain red, the remainder stain



**Fig. 5.** *A*, A cell cluster in normal cervical smear during pregnancy. *B* and *C*, Premalignant cells (precancer cell complex or dyskaryotic cells). In addition, the lower cell in *B* displays a paranuclear halo (superficial membrane defect of the cell). *D*, A malignant cell from invasive squamous cell carcinoma of the cervix.

blue-violet. In normal pregnancy, the nuclei are larger than usual and, occasionally, somewhat elongated. Granulated chromatin is distinct. The cells form clusters and are frequently folded; some typical navicular cells can also be observed. Debris, leukocytes, and *Bacillus vaginalis* of Döderlein are often observed with the cells (Figs. 4, A and 5, A).

#### Endometrial brush smears and breast

secretion smears. Both accept TMK-101 stains readily.

**Nongynecologic smears.** TMK-101 mixture can be used in the staining of nongynecologic smears. The diagnostic value of this technique has been demonstrated in smears obtained from the skin, throat, mouth, scalp, tongue, stomach, and prostate. Smears obtained through biopsy or

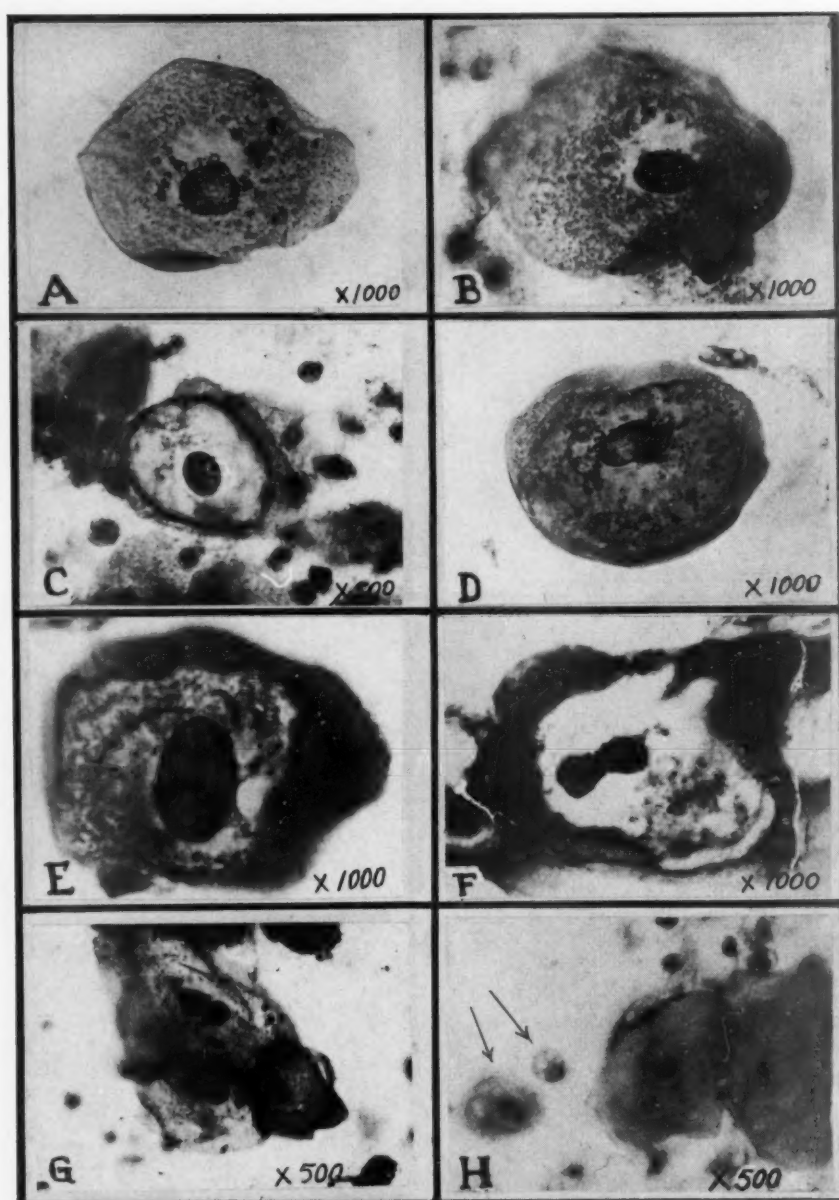


Fig. 6. A, B, and D, Fine details of cytoplasm and nucleus stained in TMK-101 4 per cent solution. C, E, and F, Paranuclear halos (the superficial membrane defect). G, A cell cluster with dumbbell-shaped nuclei from precancer cell complex or dyskaryotic changes of the cervix. H, Two trichomonads (arrows) and two squamous cells.

autopsy also stain satisfactorily.<sup>5</sup>

**Cornification.** The smear stained in TMK-101 solution usually shows slightly higher cornification or red-stained cell percentage. For example, instead of showing 50 per cent red-stained cells, as seen in Papanicolaou-stained smears, those dyed with TMK-101 show approximately 60 per cent red-stained cells.

**The paranuclear halo in smears.** With the TMK-101 staining technique, the nature of some types of paranuclear halos which are usually associated with the precancer cell complex<sup>1-3</sup> has been studied. Two groups of halos were observed: (1) an inner halo characteristic of trichomonas infection or as seen in some malignant cells; (2) the superficial membrane defect or paranuclear halo.<sup>6-8</sup>

**Phase contrast microscopy.** In slides stained with TMK-101, cells were much more easily observed, and differentiation was less difficult. All cellular characteristics observed in fresh, unstained material may be seen equally well under the phase contrast microscope in specimens stained with TMK-101. In fact, the multicoloration of such material is of great value, both in diagnostic and in research procedures, since the brilliant coloring brings into sharp relief many cellular details which remain indistinct in unstained material.

#### Comments

In the TMK-101 staining technique, there is no need for fixation, drying, or heating for mounting. The cells are observed while floating (suspended) in the staining solution. The nuclei retain their natural fluid. Cells stained in TMK-101 solution retain osmosis and diffusion, as in the normal state. Thus, they are seen in three-dimension.

The classification of cells stained with TMK-101 for simple diagnostic purposes may be divided into 4 groups: (1) normal; (2) inflammatory; (3) anaplastic (precancerous or dyskaryotic); and (4) cancerous.

Thus, the malignant growth can be diagnosed readily.

Nuclear shape, size, and hyperchromatism are important factors in cellular diagnosis. Since the substance which absorbs and retains the dye is the chromatin, the cells or nuclei which have more chromatin stain a darker color (Figs. 3, *B* and *D*; 4, *B*, *C*, and *D*; 5, *B*, *C*, and *D*; 6, *B*, *E*, *F*, and *G*).

The nuclei, in all conditions, when stained in TMK-101, show more regular form (round, oval, or slightly indented) than those stained after fixation.

The regularities of nuclei stained in TMK-101 are normal. The irregularities and deep indentations observed in nuclei treated by fixation, dehydration, and mounting in heated balsam are probably artifacts resulting from severe physiochemical treatment. Thus, after staining, the scientist, physician, or cytologist examines only cell "skeletons." Cells treated in accordance with the proposed method are much like living cells in size, shape, contour, and nuclear and cytoplasmic content.

**1. Normal superficial squamous cells.** In these, the nuclei are pyknotic, and the chromatin is condensed in a small area (Fig. 3, *A*); thus, they do not appear light.

**2. Inflammatory conditions.** The cells and nuclei, in particular, are edematous (Fig. 4, *B* at the center). Thus, they appear large, fuzzy, and light in color; but, the most prominent part of the fuzzy nucleus is the nucleolus.

**3. Anaplastic cells.** These cells are very characteristic with large, slightly irregular, and darkly stained nuclei. The nuclear membranes are thick; the chromatin content of the nuclei is irregular in size and shape, and stains very dark (Fig. 2, precancer cell complex; Figs. 4, *B*; 5, *B* and *C*; 6, *B*, *E*, *F*, and *G*). In the anaplastic cell, nuclei usually present a dumbbell appearance (Figs. 5, *C*; 6, *F* and *G*).

**4. Malignant cells.** The nucleocytoplasmic ratio is, as a rule, greater than in other cells. The cytoplasm is tiny or filmy and the nuclei are relatively larger, darker, and frequently more irregular than those seen in other conditions (Fig. 2, right side; Figs. 3, *B* and *D*; 4, *C* and *D*; 5, *D*).

### Advantages

The advantages of the TMK-101 method may be summarized thus:

1. The TMK-101 mixture is one unit; it is easily preserved for an indefinite period in a dark bottle.
2. No fixation is necessary.
3. Colorful staining is extremely rapid.
4. Mounting medium is the same dye solution.
5. The diagnostic value of smears is identical to that of smears prepared according to other more tedious cytologic staining methods.
6. The TMK-101 technique is economical, both for the physician and patient.
7. It may be used in the office of any physician.
8. If this method were adapted to private office use, cytology centers could devote more time to graded cases and research.
9. In positive or suspicious cases, the physician may send the same slide to the cytology center for a second staining by the Papanicolaou method, for confirmation purposes, when desirable or necessary. For this purpose, the mounted slide (spatula smear) must be replaced in TMK-101 solution. The cover slip is easily removed. The slide is then removed from the staining jar and replaced in fixative (50 c.c. absolute alcohol and 50 c.c. ether); after 30 minutes the slide is removed; a few drops of glycerine is added to the smear and it is covered with another clean slide, then packed for mailing (Ayre's glycerine mailing technique).<sup>4</sup> The TMK-101 technique changes neither the quality nor the quantity of the cells and nuclei. The slide can be restained by the Papanicolaou method. However, if necessary, while the physician is examining the first smear, the patient will still be present, and

another smear may be made for forwarding to the cytology center.

10. TMK-101 stains not only are useful in cancer detection, but we believe that they will also prove advantageous in other cytologic studies because their staining capacity is great and they do not destroy fine cellular detail.<sup>9</sup>

11. This method can easily replace phase contrast microscopy when it is used for diagnostic purposes in the private physician's office. The slide stained in TMK-101 can also be studied in the laboratory under the phase contrast microscope for scientific purposes. The coloration helps in location and differentiating between cells. In fact, after the smear stained with TMK-101 is seen, there is no need to study by phase contrast microscope. The result with an ordinary microscope is almost identical to phase contrast microscopy.

### Summary

A new dye mixture, designated as TMK-101, which is used in the preparation of fresh smears without fixation and which is useful in cytologic cancer diagnosis and research, has been presented.

This new technique, the TMK-101, Türk, staining method, is simple, inexpensive, and easily applied to cytologic smears.

For diagnostic work, the method is of considerable value, especially in general and gynecologic office practice where the rapid staining of cervical smears is desirable.

The author acknowledges, with thanks, the kind and encouraging help of J. Ernest Ayre, M.D., Director of the Cancer Institute at Miami, during the course of these investigations at the Institute; also, to Miss M. D. Bellomy for assistance in the preparation of this manuscript.

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## CURRENT OPINION

### Re-evaluation

## "Spasm" in uterotubal insufflation

HERBERT F. NEWMAN, M.D.

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IN HIS monograph, Rubin<sup>1</sup> reported "spasm" in 7.9 per cent of 30,557 collected cases of uterotubal insufflation where some patency was present. To it has been attributed the phenomenon of the "adoption baby" where a presumably sterile woman became pregnant shortly after adopting an infant, and I have observed two women who became pregnant despite a diagnosis of sealed tubes as established by repeated gas insufflations.

Usually a neuromuscular mechanism for spasm, analogous to that in the bowel, is postulated. In 1895, Langley and Anderson<sup>2</sup> reported that electrical stimulation of the sympathetic trunk in the rabbit is followed by marked blanching and contraction of the homologous uterus with coincidental hyperactivity of the tube. To determine whether or not these motor movements altered the luminal area of the tube, Dr. I. C. Rubin and I repeated these studies in rabbits undergoing uterotubal insufflation and the results are here published for the first time. A thyatron discharge of 4 volts intensity and frequency of 200 to 300 per second was used for stimulation with a bipolar electrode. Each experiment was repeated in 25 virgin rabbits and the results were uniform in all animals.

*From the Union Health Center.*

1. Direct stimulation of the body of the uterus did not affect the pressure tracing, whereas application of the electrode to any portion of the tube caused an immediate rise in insufflation pressure (Fig. 1, *A* and *B*). Although not germane to this study, support is lent to the theory that the fluctuations in perfusion pressure during insufflation are tubal rather than uterine in origin, if we consider the cornual segments as properly tubal rather than uterine in nature.

2. Stimulation of the mesentery of the tube or uterus produced no change except over the uterine or ovarian vessels with their perivascular nerve plexi (Fig. 1, *C*, *E*, and *F*). The rises in pressure could be blocked by the injection of procaine into these areas. The pedicle containing the ovarian vessels and nerves was divided. Stimulation of the proximal end of the divided stump produced no pressure change, whereas the usual rise was observed when the distal stump was excited (Fig. 1, *X*, *G*, and *H*).

3. Stimulation of the periaortic nerve plexus at the level of the third lumbar vertebra caused a slight rise in pressure (Fig. 1, *D*).

4. Stimulation of the homologous sympathetic chain at the level of the third lumbar vertebra caused an enormous rise in pressure. The trunk was divided at this location, and once again stimulation of the proximal end

was ineffectual, whereas maximal rises in pressure followed excitation of the distal end (Fig. 1, I, Y, J, and K). In two instances, tubal closure was so powerful that the rabbit's thin-walled uterus ruptured at about 200 mm. Hg pressure.

These results from experiments with animals are suggestive evidence substantiating the existence of spasm of neurogenic origin but cannot be directly transferred to man.

Hypnosis is a useful experimental tool for inducing temporary, controlled alterations in "affect" and the study of psychomotor phenomena. Two normal female volunteers were found to be good subjects. In both women, after a control period of 3½ minutes of insufflation, hypnosis was rapidly induced

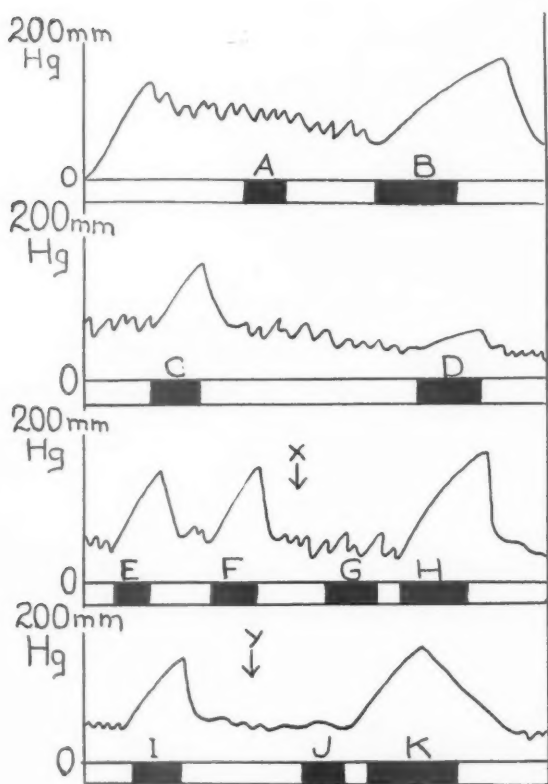


Fig. 1. Stimulation of body of uterus (A), tube (B), uterine vessels and nerves (C), periaortic plexus (D), ovarian vessels and nerves (E, F), proximal end of divided ovarian pedicle (G), distal end of divided ovarian pedicle (H), sympathetic trunk (I), proximal end of divided sympathetic trunk (J), and distal end of divided sympathetic trunk (K). Division of ovarian vessels and nerves (X). Division of sympathetic trunk at level of third lumbar vertebra (Y).

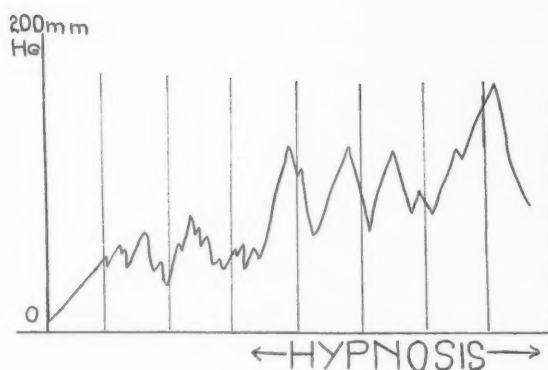


Fig. 2. The effect of hypnosis on the insufflation tracing in a woman with normal Fallopian tubes.

and the suggestion of complete muscular relaxation and insensitivity to pain was offered. The entire body became flaccid and did not respond to the usual painful stimuli. It was hoped that the tubal musculature would also partake in the somatic muscular relaxation with a fall in pressure toward the base line. On the contrary, a bizarre pressure tracing followed with slow, huge waves replacing the normal shallow oscillations (Fig. 2). There was no visible alteration in respiration on abdominal muscular activity which could explain these peculiar psychically induced contraction patterns.

Spasm is postulated on gas insufflation when one of two pressure tracings appear: (1) complete block at 200 mm. Hg pressure at one examination with patency at lower levels on subsequent testing; (2) the pressure at the start of insufflation rises above 100 to 150 mm. Hg but rapidly falls to a much lower plateau level upon which are superimposed small fluctuations.

Mechanical artifacts may be responsible for both types of tracing. Polak<sup>3</sup> suggested that the gas pressure may push the mucosal folds of the tube together and obturate the lumen. Rubin<sup>1</sup> thought sharp flexions of the body of the uterus may cause mechanical pressure artifacts. Patency is often not obtained by repeated insufflations of gas at a head of 200 mm. Hg, whereas radiopaque, aqueous dyes revealed normal salpingograms although the fluid was injected with slight force. In our experiments in rabbits, transitory complete block or a high primary pres-

sure peak were often observed with insufflation of gas but never when fluid formed the perfusion medium. In 5 consecutive humans who demonstrated a high primary pressure peak with carbon dioxide, insufflation was immediately repeated with normal saline solution and a strain gauge manometer. In each case, fluid entered the peritoneal cavity without a primary pressure peak but at the usual plateau level, i.e., below 60 mm. Hg. A similar phenomenon is elicited when excised fetal atelectatic lungs are inflated. It requires two and a half times as much pressure to expand the lung with air as with fluid.<sup>4</sup> The explanation is probably the same

in both instances—surface tension between moist apposing surfaces.

Therefore, although the presence of a neuromuscular mechanism affecting tubal patency is substantiated by animal studies and may explain "spasm" in some cases, the diagnosis must be made with caution when based on gas insufflation alone. Insufflation with saline or aqueous radiopaque dye under manometric control will eliminate some mechanical artifacts produced by surface tension.

I wish to acknowledge the kind assistance of Dr. Sidney Orens, who performed the hypnosis.

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# Distortion of the birth frequency curve

PETER D. KING, M.D.\*

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I HAD previously reported<sup>1</sup> an increased frequency of births in the morning hours. By dividing the day into two 12 hour periods—12 P.M. to 12 A.M. and 12 A.M. to 12 P.M.—the incidence of A.M. births among

**Table I.** Number of births each hour of the day in five hospitals

Time	No. of births
<i>Group A</i> (3 A.M. to 11 A.M.)	
3	1,590
4	1,560
5	1,632
6	1,547
7	1,470
8	1,588
9	1,585
10	1,515
<i>Group B*</i> (11 A.M. to 3 P.M. and 11 P.M. to 3 A.M.)	
11	1,416
12	1,355
1	1,297
2	1,281
11	1,335
12	1,422
1	1,418
2	1,480
<i>Group C</i> (3 P.M. to 11 P.M.)	
3	1,134
4	1,276
5	1,180
6	1,213
7	1,103
8	1,267
9	1,298
10	1,253

\*In the original publication of this table the figures in Group B were inadvertently shuffled. The original findings are correctly listed here.

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my 33,215 cases was 54.9 per cent and the incidence of P.M. births was 45.1 per cent, an extremely significant difference (Table I).

In order to study the possibility of an influence of geographic latitude on birth frequency, 10,469 Caucasian births in the Medical College of Virginia Hospital, Richmond, Virginia (MCV) and 13,266 Negro births in the St. Philip's Hospital, Richmond, were tabulated by hour of day. St. Philip's Hospital showed 53.3 per cent of its births in the A.M. and 46.7 per cent in the P.M., a difference which is extremely significant statistically and which is similar to my earlier data. A curve of the indices\* (Fig. 1) was also similar to the curve of the indices of my earlier data, as were the individual curves of the indices of each of the five hospitals reported before. The curve derived from the MCV Hospital births was markedly different, however. It showed a distinct peak in the early afternoon hours, and the difference of each hour between this and my earlier data totaled 30.2 per cent. Correspondence with the obstetrical chief of MCV revealed that approximately 15 per cent of deliveries are induced—usually by rupture of the membranes. Assuming that this 15 per cent of births shows an excess over my earlier data, there will be a corresponding deficiency of births of 15 per cent at another time of day. The total of excess and deficiency is 30 per cent, and compares favorably with the 30.2 per cent difference which was observed.

Since artificial rupture of the membranes is done almost exclusively in private patients

\*Each index was obtained by taking the percentage of total births in a hospital occurring each hour and multiplying by 100.

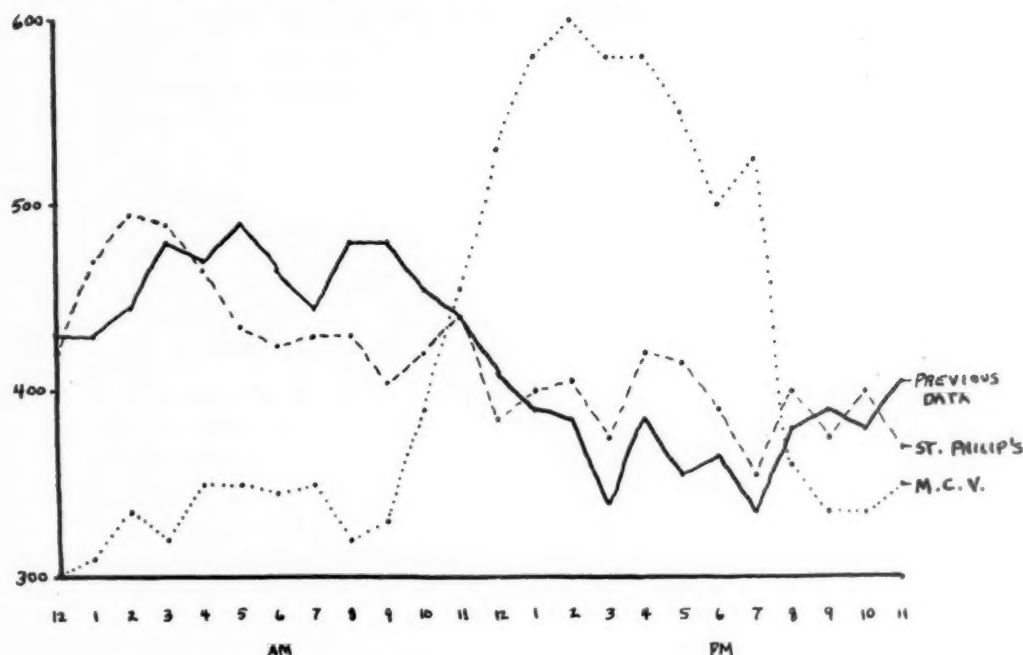


Fig. 1. The number of births plotted by the hour of the day, indicating the marked shift which presumably represents the effect of the elective induction of labor in the private hospital.

in these two hospitals, and since approximately 75 per cent of MCV patients are private while only 5 per cent of St. Philip's patients are private, a reasonable explanation for the observed difference of indices between these two Richmond hospitals is obtained.

### Summary

In summary, births at a Negro hospital showed a frequency distribution throughout

the 24 hours similar to earlier data, while a White hospital in the same city showed a significant difference. This difference may be explained by an induction of labor by rupture of the membranes in at least 15 per cent of deliveries in the White hospital.

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# Anemia in pregnancy

ROY G. HOLLY, M.D.

*Omaha, Nebraska*

IT HAS been my privilege to have participated in the formulation of some of the current concepts pertaining to hematopoiesis and pregnancy. Certain views which I have previously expressed have been modified or strengthened on the basis of continued investigation. I wish to briefly summarize some of these changes.

The late Dr. William Dieckmann published exhaustive studies on normal blood values for pregnant women. The "10 gram per cent hemoglobin" then was accepted as a minimum normal value. Slight or moderate decreases in the hemoglobin concentration were expected and were considered "physiologic." Dieckmann correctly emphasized the value of the hematocrit as the more accurate of the two determinations. Too few of our colleagues have accepted this important fact, for it is usually far simpler to obtain the hemoglobin.

It is my belief that the 10 Gm. hemoglobin and corresponding 33 per cent hematocrit are too low to accept as normal and minimum in pregnancy. This conviction is based on the following evidence: First, the changes in the serum iron, iron binding capacity of the serum, and the erythrocyte protoporphyrin when the hemoglobin falls below 11.5 Gm. per cent are consistent with an iron deficiency state. Second, storage iron estimates by means of a bone marrow biopsy have demonstrated that these iron reserves are depleted when the hemoglobin is decreased below 11.5 Gm. per cent. Third,

the administration of an adequate iron supplement will maintain normal hematologic values throughout pregnancy. In summary, hematologic norms established for the nonpregnant woman apply for pregnancy as well!

The relationship of iron to hematopoiesis during pregnancy has been the subject of investigation in my laboratory for several years. My views on this relationship have been modified to take into account the shifts of iron within the two major depots of body iron and the relatively large demand for iron by the growing fetus. Let us consider each of these points individually.

The fetal demand for iron has been estimated to represent 400 to 500 mg. of the element, a quantity of iron that most women can ill afford to lose. This estimate is based on ashing techniques in which stillborn infants were studied. The fetus contains approximately 375 mg. of iron. To this amount we can add 50 to 100 mg. of iron which represents placental iron and that iron in the blood trapped within the placental vessels. The iron transferred to the products of conception is at least one eighth of the total maternal body iron pool. The fetus is supplied its iron at the expense of all other maternal iron depots so, if the storage depots and the dietary intake are insufficient to meet the fetal demands, iron is shifted from the maternal hemoglobin pool. This means iron-deficiency anemia.

Hemoglobin mass may be defined as the total circulating hemoglobin. It is known that the total blood volume increases dur-

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Table I

Blood volume (ml.)	4,000	5,000
Hemoglobin (Gm.%)	13	13
Hemoglobin mass (Gm.)	520	650
Hemoglobin iron (mg.)	1,768	2,210
Iron needed (mg.)		442

ing pregnancy. For the hemoglobin concentration (grams per cent) to remain constant and normal, there must obviously be an increase in the hemoglobin mass. Iron is required for the synthesis of this extra hemoglobin at the rate of 3.4 mg. per gram of hemoglobin. In Table I, I have indicated the amount of iron necessary to maintain a hemoglobin concentration of 13 Gm. per cent under circumstances where the total blood volume increases from 4,000 to 5,000 ml.

Under these conditions, 442 mg. of iron is necessary to provide the means by which the pregnant woman may maintain a normal hemoglobin concentration. The total amount of "available iron" necessary to provide for the fetus and the extra hemoglobin mass is at least 800 mg.

Available iron is that iron stored in the liver, spleen, and bone marrow. It is also the iron absorbed from the diet. Of the two sources of available iron, the storage iron pool is by far the more important unless the diet is supplemented by means of an iron salt. If the storage iron is normal (approximately 1,000 mg.) there is sufficient iron for all the requirements of pregnancy, and the hemoglobin concentration remains normal. Our studies in which the amount of storage is estimated by bone marrow biopsy have demonstrated that iron is gradually withdrawn from the storage area to meet the iron requirements of pregnancy. These studies have revealed that few women begin pregnancy with normal iron reserves. In summary, pregnancy creates a situation in which the growing fetus gradually siphons off iron from the maternal supply. Iron must be available for extra hemoglobin synthesis if the maternal hemoglobin concentration is to remain normal. The iron

for these requirements is available from the iron reserves or through the intestinal mucosa as absorbed iron.

The mechanism by which iron is absorbed is poorly understood. Only the ferrous iron is absorbed and only in small quantities. A normal diet contains from 8 to 12 mg. of iron and but a small fraction of this can be absorbed. Our studies have demonstrated that a normal diet provides insufficient iron to prevent withdrawal of iron from the storage depots. It is estimated that no more than 1.5 to 2 mg. of iron is absorbed daily from a normal diet. This is not sufficient for pregnancy requirements. All of the evidence available indicates the diet of every pregnant woman should be supplemented with an iron salt!

My views on the types of anemia which may be encountered during pregnancy have been altered in placing greater emphasis on the anemia of infection. Chronic infection blocks normal hemoglobin synthesis. The anemia is characterized by the low hemoglobin, a low serum iron, and hypochromic erythrocytes. Iron therapy is ineffective. Unlike iron-deficiency anemia, which it closely resembles, in the anemia of infection the iron-binding capacity of the serum is low and storage iron can be demonstrated. Appropriate antibiotic therapy releases the marrow inhibition, the iron reserves are mobilized, and repair proceeds at a rapid rate.

I have previously referred to marrow "hyperplasia" and, more recently (AM. J. OBST. & GYNEC. 77: 741, 1959), have used the term "hypoplasia." This is not a reversal requiring re-evaluation, however, but a confusion in nomenclature since we do not differentiate between the histologic appearance of the marrow (which is usually a hyperplasia) and the red cell production rate (which may be relatively diminished during pregnancy). The two concepts are compatible in my mind. As an example, a nonpregnant individual with aplastic or hypoplastic anemia may have a hyperplastic marrow with a marked decrease in red cell production.



## Editorial

### The publication of translations of articles from the Russian

ON PAGE 244 of the current number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there appears an article entitled "Stillbirth and Ways to Reduce It," by V. A. Kuznetsov and A. B. Sigalov, reprinted from the journal, *Soviet Medicine*. The reprinting of this article constitutes a perhaps temporary experiment by the editors of the JOURNAL in presenting to its readers some selections from the Russian obstetrical and gynecological literature.

The first step toward the publication of this material was taken in the late fall of 1956, when the AMERICAN JOURNAL, with undoubtedly many others, received a letter from the Director of the National Institutes of Health suggesting that we participate in an effort designed to inform American scientific workers about recent Soviet contributions to the medical sciences.

There followed a number of months, and indeed a year or two, when the editors of the AMERICAN JOURNAL were hesitant to use any of their rather precious pages for the republication of articles from a foreign language. However, it remains evident that access to Russian language publications is not possible for the vast majority of our readers and interest in what is going on in Russia has consistently increased.

Accordingly, about 6 months ago the subject was reopened with the Director of the National Institutes of Health and the process of selecting suitable material set in motion. Certain definite steps have been followed in order to pick what is of greatest interest.

Through the *Excerpta Medica Foundation* we have received advance *Abstracts of Soviet Medicine* and, having read the brief synopses of some hundred articles, have submitted to the National Institutes of Health the titles of 8 articles of which we would like to read the complete translations. The one selected is the first translation which we have received.

The present selection is not being reprinted because it contains ideas of startling originality or merit. Its interest seems to rest largely in the obvious fact that the increasing interest in the fetus and the newborn, so evident in the United States in the last few years, is being paralleled by an increasing attention to the problem in the Soviet Union. The importance of "protracted dry labor" and of transverse positions as causes of stillbirth will come as a surprise to most American obstetricians and the proper names applied to methods which almost certainly have their counterparts in America lend an interesting foreign flavor to the article, even in translation.

The editors will continue to read *Abstracts of Soviet Medicine* and with the assistance of the National Institutes of Health will present at least a short series of such translations, continuing until it is determined whether the experiment is worthwhile enough to make it a permanent feature of the JOURNAL.

H. C. T.  
J. I. B.  
A. C. B.

## Reviews | Abstracts

*Edited by*

LOUIS M. HELLMAN, M.D.

### Reviews of new books

**Office Gynecology.** By J. P. Greenhill. Seventh edition. 230 illustrations, 145 figures, 572 pages. Chicago 1959, Year Book Publishers, Inc. \$9.00.

This seventh edition of *Office Gynecology* contrives to serve as a practical guide to office operative and nonoperative gynecologic procedures. It serves as a comprehensive and up-to-date guide for all men in practice.

Three new chapters have been added: "Office Pediatric Gynecology," "Office Geriatric Gynecology," and "Intersexuality." The latter deals with the classification of intersexuality and diagnosis from history, and physical examination, as well as sex chromatin patterns and hormone assays and the management of intersexuality.

There has been new data added on endocrinology, pelvic tuberculosis, and office urology. The chapters on culdoscopy, obesity, psychosomatic gynecology, backache, and office proctology are informative.

**Fisiopatologia del ovario restante.** By R. Pecorone. 196 pages, 14 tables, 14 figures, 13 graphs. Rosario, Argentina, 1959, Ginecologo de Instituto de Ginecologia del Sanatorio Britanico.

Whether or not to perform bilateral oophorectomy at the time of hysterectomy is dealt with in this short work. The subject is approached by a detailed review of both clinical and experimental articles regarding the study of ovarian function in humans and in animals who have had hysterectomy. In addition, the author also adds the results of his own clinical experience. He concludes that pathological ovaries should be removed at the time of hysterectomy. This implies that the surgeon be well founded in the recognition of gross ovarian pathological conditions. Furthermore, in order to make an intelligent decision, the physician should evaluate ovarian function preoperatively. If one elects to leave the ovaries in women at the time of hysterectomy, then one should be meticulous about preserving the blood supply of the ovaries. He also concludes that if one is going to leave ovaries in, then one should leave both ovaries instead of electively removing a single normal ovary. He feels that leaving both ovaries does not double the risk of carcinoma. The book is well written and handles this most important and provocative subject very well.

### Selected abstracts

#### **Acta Anatomica**

*Vol. 38, 1959.*

Fredricsson, Bengt: Studies on the Morphology and Histochemistry of the Fallopian Tube Epithelium, p. 1.

#### **Journal of Clinical Endocrinology and Metabolism** *Vol. 19, March, 1959.*

\*Eglin, J. M., Jr., and Jessiman, A. G.: Inactivation of the Antidiuretic Activity of

\*These articles have been abstracted.

Vasopressin During Pregnancy, p. 369.  
**Eglin and Jessiman: Inactivation of the Anti-diuretic Activity of Vasopressin During Pregnancy, p. 369.**

A case is reported in which severe diabetes insipidus occurred following hypophysectomy performed for carcinoma of the breast in a pregnant patient. During pregnancy the diabetes insipidus could not be controlled by relatively large doses of vasopressin. Following parturition, the necessity for administration of vasopressin ceased by the ninth day.

A study is described in which a physiologic dose of vasopressin was administered intravenously under standard conditions of water diuresis in the pregnant and postpartum periods. The shorter duration of negative free water clearance that was noted during pregnancy is attributed to the destruction of vasopressin at an increased rate. Presumably, endogenous anti-diuretic hormone was being similarly destroyed. It is suggested that this is due to a circulating enzyme elaborated by the placenta. Recurrence of the polyuria was noted in the preterminal period. This could readily be controlled by the administration of vasopressin.

*J. Edward Hall*

*April, 1959.*

\*Venning, E. H., Dyrenfurth, I., Lowenstein, L., and Beck, J.: Metabolic Studies in Pregnancy and the Puerperium, p. 403.

**Venning et al.: Metabolic Studies in Pregnancy and the Puerperium, p. 403.**

Metabolic balance studies, determinations of body fluid compartments, and measurement of urinary corticosteroid excretion were carried out in 5 pregnant women during the latter part of gestation and immediately post partum. During the study, significant storage of nitrogen and cellular volume occurred in the antepartum period. The accelerated weight loss following delivery may have been in part associated with the restoration of body fluid compartments to normal. Negative nitrogen and potassium balances were observed at this time, associated with a rise in the levels of serum nonprotein nitrogen and potassium. Sodium storage was most marked in the antepartum period and continued to a lesser degree in the postpartum period when the over-all sodium balance was considered for this part of the study. Sodium diuresis was always observed soon after delivery.

The establishment of a new metabolic equilibrium

had not occurred by the time of cessation of these studies. In the antepartum period there was an apparent correlation between sodium retention and aldosterone excretion. Immediately post partum, variations in sodium excretion were also associated with changes in aldosterone excretion, but later in the postpartum period aldosterone excretion returned to nonpregnancy levels and did not vary with further changes in the sodium balance. An increase in total blood volume, extracellular fluid volume, plasma volume, and total body water was observed in the antepartum period. There was a postpartum reduction in these parameters and the data suggest that it may have been partly due to the alterations in aldosterone secretion.

*J. Edward Hall*

\*Borglin, N. E.: Serum Transaminases in Toxemia of Pregnancy, p. 425.

**Borglin: Serum Transaminases in Toxemia of Pregnancy, p. 425.**

Determinations were made of the serum glutamic-oxalacetic transaminase and serum glutamic-pyruvic transaminase levels in patients with toxemia of pregnancy and in pregnant women with symptoms of liver damage supposed to be secondary to the pregnant state. The transaminase value was found to be high in about 30 per cent of the former and in more than 50 per cent of the latter. The only demonstrable relationship between a high transaminase value and clinical symptoms or other laboratory findings was the correlation with signs of coexisting liver disorder or damage.

The assumption that the increase in transaminase activity is due to hepatocellular damage is also supported by the observation that the increase in the serum glutamic-oxalacetic transaminase value was usually accompanied by an increase in the serum glutamic pyruvic transaminase value and that in some cases only the latter was increased above the normal level.

*J. Edward Hall*

**Journal of the Philippine Medical Association**

*Volume 34, November, 1958.*

Songco, R. S., de Leon, M. G., de Leon, A. S., and Lopez, R. N.: Bilirubin Levels During the First Days of Life, p. 657.

**Lancet***Vol. 1, April 18, 1959.*

\*Ashworth, Audrey M., and Neligan, Gerald A.: Changes in the Systolic Blood Pressure of Normal Babies During the First Twenty-four Hours of Life, p. 804.

\*Bennett, Marjorie, and Mather, Gordon: Phaeochromocytoma in Pregnancy, p. 811.

**Ashworth et al.: Changes in the Systolic Blood Pressure of Normal Babies During the First Twenty-four Hours of Life, p. 804.**

The blood pressure of 20 babies who were considered to be normal in every respect was studied repetitively during the first day of life. In every instance the blood pressure fell. The mean fall was 32 mm. Hg (range 14 to 54 mm.). The highest readings which were obtained within 15 minutes of delivery in every instance except in one baby whose cord was not clamped for 20 minutes and in whom a secondary rise was observed ranged between 62 and 116 mm. Hg (mean, 92 mm. Hg). The lowest readings were recorded within 4 hours after delivery in the 8 babies whose cords were clamped early. In the 12 infants whose cords were clamped later the maximal fall was delayed but always occurred with the first 24 hours. The lowest readings ranged between 44 and 76 mm. Hg (mean, 60 mm. Hg). During the remaining days of the first week of life the steady rise in systolic blood pressure that has been reported previously was confirmed. Although both the systolic blood pressure and body temperature fall and later rise there was no constant relationship between them nor was any constant relationship found between pulse rate and blood pressure. Delay in clamping the cord, to enable blood to be transferred from the placenta to the baby's circulation, postponed the fall but did not affect its magnitude. In 7 of the 12 infants whose cords were not clamped immediately after delivery there was a delayed rise in blood pressure which reached a peak between 2½ and 13 minutes after the cord was clamped. This rise did not appear to be due to "placental transfusion" because in some instances the secondary rise occurred after the blood pressure had been found to be falling rapidly. Anoxemia also did not appear to be a reasonable explanation. Perhaps a vasopressor mechanism as postulated by C. A. Smith (*The Physiology of the Newborn Infant*, Springfield, Ill., 1951, Charles C Thomas, publisher, p. 102) may be responsible.

David M. Kydd

**Bennett and Mather: Phaeochromocytoma in Pregnancy, p. 811.**

Two patients who were pregnant when the diagnosis of pheochromocytoma was made. The first, aged 29, who had symptoms for 2 years, developed a blood pressure that fluctuated widely. Fetal death occurred at about 28 weeks' gestation and 2 weeks later the patient died suddenly. Postmortem examination disclosed a macerated fetus and a pheochromocytoma of the left adrenal gland in which a hemorrhage had occurred. The second patient, also aged 29, developed hypertension and sweating during the sixth month of her fourth pregnancy. A pheochromocytoma was suspected and the blood pressure fell markedly following the administration of phentolamine. Because of the severity of her condition she was operated upon and a left-side adrenal tumor was removed. The catechol amines in the tumor were estimated to be 21 mg., of which 95 per cent was noradrenaline. Subsequently, the blood pressure was stable and she felt well. Six weeks after the operation she was delivered of a living female child weighing 5 pounds, 4 ounces. Six months later she appeared to be well although many retinal scars remained. The association of pheochromocytoma and pregnancy has been reported to be not rare and the mortality has been 50 per cent, with most of the deaths occurring soon after delivery because of hypertensive crisis. Only 2 patients have been reported previously who have been operated upon during the course of pregnancy because of pheochromocytoma.

David M. Kydd

*April 25, 1959.*

\*Tovey, G. H., Gillespie, E. M., Guy, J., Valaes, T., Oppe, T. E., and Lewis, F. J.: Cord-Blood Findings in ABO Haemolytic Disease, p. 860.

\*Malcolm, J. E., Vernon, F. L. A., Merrifield, A. J., and Beatson, T. R.: Fulminating Eclampsia Treated by Hypothermia, p. 863.

Fraser, G. R., Harris, H., and Robson, E. B.: A New Genetically Determined Plasma-Protein in Man, p. 1023.

**Tovey et al.: Cord-Blood Findings in ABO Haemolytic Disease, p. 860.**

The authors' practice is to examine the mother's serum for hemolysins when there is a history of a previous baby being severely jaundiced or



stillborn and the father's blood is of an incompatible ABO group. Should hemolysins be present, oxalated and clotted samples of cord blood are tested to determine the extent of the disease. Cord bloods are tested also when an exceptionally potent anti-A or anti-B hemolysin is found by chance during either a first pregnancy or a pregnancy when other children have been normal.

In this study the cord blood obtained from 575 babies was studied. In 393 samples the baby's blood group was O ("compatible") and in 182 it was A or B ("incompatible"). The incidence of slight jaundice (less than 10 mg. bilirubin per 100 ml.) was the same in the compatible and the incompatible group, but severe jaundice was more frequently found in ABO incompatible babies. Maturity appeared to be a factor, for, of 450 full-term babies, 8 per cent of ABO incompatible babies became deeply jaundiced compared with 1 per cent of compatible babies, of 92 babies immature by age of gestation but weighing more than 2,500 grams, as many as 19 per cent became deeply jaundiced but the influence of ABO incompatibility had disappeared (20 per cent of the compatible babies and 16 per cent of the incompatible babies); and, of 33 premature babies, 6 of the compatible ones became jaundiced and but one of the incompatible. Six of the 575 babies had ABO hemolytic disease and each, with one exception, became jaundiced within 24 hours of birth. The early appearance of jaundice in an infant without Rh or other blood incompatibility was the only consistently reliable sign of ABO hemolytic disease, for neither the value of serum bilirubin in cord blood, saline fragility, reticulocytosis, or direct antiglobulin test proved to be useful. The only laboratory finding common to each of the 6 cases was the presence of an anti-A or anti-B hemolysin in the mother's serum. None of these babies with ABO hemolytic disease needed exchange transfusions, but in other instances severe jaundice requiring transfusion, has developed. Inasmuch as the cord blood gave no predictive information as to the need for exchange transfusion, the serum bilirubin must be repeatedly determined and exchange transfusion carried out if the value of bilirubin becomes dangerously high.

David M. Kydd

**Malcolm et al.: Fulminating Eclampsia Treated by Hypothermia, p. 863.**

A patient, aged 23, was admitted in the thirty-fifth week of pregnancy because of coma and convulsions. Although the blood pressure was not significantly raised and the retinae were normal, she had edema of the ankles and legs and albuminuria. A cesarean section was performed and the child, who weighed 5 pounds, did well after having had a few mild fits. The mother did not regain consciousness and continued to have convulsions. She received pethidine, chlorpromazine, and promethazine without effect. Because her condition became worse and because her symptoms resembled those seen following head injuries, the institution of hypothermia was undertaken. Following a tracheotomy (nitrous oxide, oxygen, and halothane anesthesia) she received a saline infusion containing pethidine, chlorpromazine, promethazine, heparin (to prevent clotting), and cortisone (to prevent thrombosis). The patient was cooled by exposure to cold air from an electric fan. The convulsions ceased when she was anesthetized before the tracheotomy. The following day her temperature had reached 92° F. She regained sufficient consciousness to recognize her husband. Further cooling was stopped and the process discontinued the following day. Moderate diuresis commenced when cooling was well established. Two days later when her temperature reached normal she received chlorothiazide and developed a profound diuresis. The edema subsided and she recovered apparently completely.

David M. Kydd

May 2, 1959.

\*Bevan, Beryl: Haemolytic Disease of the Newborn Caused by Anti-Duffy (Fy<sup>a</sup>), p. 914.

\*Yeates, W. K., and Durh, M. S.: Palliation in Vaginal Urinary Fistula, p. 916.

**Bevan: Haemolytic Disease of the Newborn Caused by Anti-Duffy (Fy<sup>a</sup>), p. 914.**

Early in the course of her sixth pregnancy the serum of a woman who was known to belong to blood Group O, Rh negative, was tested and found to contain rhesus antibodies active in saline, albumin, and by the anti-human globulin technique against all rhesus positive cells. Previous pregnancies resulted in: (1) a premature infant who died shortly, (2) a macerated premature infant, (3) a normal infant (blood Group O, Rh negative), (4) a premature jaundiced infant with erythroblastosis (blood

Group O, Rh positive [D +]) who died a day after being given a transfusion of Group O, Rh negative blood, and, (5) a stillborn hydropic infant (blood Group O, cDE/cde, direct Coombs test positive on cord blood). Also there was a weak reaction that could be shown by the anti-human globulin technique against some rhesus-negative cells. The mother was Fy (a-) and Anti-Fy<sup>a</sup> was found to be responsible. At the eighth month of the pregnancy the mother's serum gave a much more powerful reaction. The infant was delivered at term by cesarean section and shortly became jaundiced. The cord blood was Group O, rhesus negative, the direct Coombs test was positive and the serum bilirubin was 3.6 mg. per 100 milliliter. Following a replacement transfusion with Group O, Rh negative, Fy(a-) blood, the child did well. On the 100th day the cells of the infant were shown to be Fy(a+) Group O, Rh negative. Further tests showed the following groups: mother: O, MMS, P<sub>21</sub> cde/cde, Lu(a-), K-, Le (a + b-), Fy(a+); father: O, Ms/Ns, P<sub>11</sub>, cDE/cde, Lu(a-), K-, Le(a+ b-), Fy(a+). In 22 per cent of all matings there is a possibility of isoimmunization by the Fy<sup>a</sup> antigen and the instance reported emphasizes the importance of testing for this antibody as well as anti-Rh and of ensuring that blood for transfusion of infants with hemolytic disease should be compatible with the mother's serum.

David M. Kydd

**Yeates and Durh: Palliation in Vaginal Urinary Fistula, p. 916.**

While waiting for local and general conditions to become optimal before repair of ureterovaginal or vesicovaginal fistula, the use of a simple apparatus inserted into the vagina consisting of a small marine sponge thrust partway into a piece of Paul's rubber in such a manner that the rubber tubing acts by suction to remove the extravasated urine has been found to be helpful in preventing irritation of the surrounding structures.

David M. Kydd

**Proceedings of the Society for Experimental Biology and Medicine**  
Vol. 100, February, 1959.

\*Luhby, A. L., Cooperman, J. M., and Donnenfeld, A. M.: Placental Transfer and Biological Half-Life of Radioactive Vitamin B<sub>12</sub> in the Dog, p. 214.

\*Thorn, N. A., and Milewski, B.: Effect of Leucine-Vasopressin (Phenylalanine-Oxytocin) on Renal Excretion of Na and K in Hydrated Rats and Dogs, p. 267.

\*Shelesnyak, M. C.: Fall in Uterine Histamine Associated With Ovum Implantation in Pregnant Rat, p. 380.

**Luhby, Cooperman, and Donnenfeld: Placental Transfer and Biological Half-Life of Radioactive Vitamin B<sub>12</sub> in the Dog, p. 214.**

The authors studied the transfer of vitamin Co<sup>60</sup>B<sub>12</sub> across the placental barrier by injecting a single subcutaneous dose 5 months prior to mating and approximately 7 months prior to delivery of the litter. The mother and Pup No. 1 were followed for 6 weeks post partum and then sacrificed, at which time the organs were measured for their content of the radioactive vitamin. Pups No. 2 and No. 3 were given small "calibration doses" 4 weeks post partum and, by measuring the change in radioactivity, the authors were able to estimate the amount of Co<sup>60</sup>B<sub>12</sub> that had been transferred placentally to the fourth pup of the litter. They found that placental transfer of the vitamin in the dog for the entire litter amounted to 20 per cent of the residual radioactive vitamin in the bitch at time of delivery. They also found that the proportional distribution of the vitamin among major organs of the mother and pups to be similar. Biological half-life of the radioactive vitamin B<sub>12</sub> averaged 2 months in the mother and pups during the postpartum period.

The authors attempt to explain, on the basis of their data, the apparent parasitization of the mother on the basis of withdrawal of the vitamin from the mother's "mobilizable stores," which are dependent on her dietary intake rather than on her tissue stores which may be highly bound. The high fetal blood levels, on the other hand, are not reflected by high fetal tissue levels. The data available do not explain this phenomenon; however, they propose that some characteristic of the placental transfer system may account for the maternal fetal plasma gradient.

Stuart O. Silverberg

**Thorn and Milewski: Effect of Leucine-Vasopressin (Phenylalanine-Oxytocin) on Renal Excretion of Na and K in Hydrated Rats and Dogs, p. 267.**

The effect of leucine-vasopressin, which can be regarded as a structural intermediate between natural vasopressin and oxytocin, on hydrated rats and dogs was studied in regard to the excretion or retention of sodium and potassium. The studies show the drug to have a physiological effect between vasopressin and oxytocin with the action of both being present. The injection of leucine-vasopressin intravenously in submaximal antidiuretic doses to hydrated dogs and rats produces an increase in the rate of urinary excretion of both sodium and potassium, proportionate to the dosage. Because of the parallel rise in K<sup>+</sup> excretion, the authors suggest that the mechanism, although obscure, is not one of interference with renal actions such as with aldosterone or other adrenocortical steroids.

Stuart O. Silverberg

**Shelesnyak: Fall in Uterine Histamine Associated With Ovum Implantation in Pregnant Rat, p. 380.**

The uteri of recently mated rats were examined for histamine content at intervals of 96, 120, and 144 hours after detection of sperm in the vagina. Both histamine content and concentration were measured and found to be markedly reduced between 96 hours and 120 to 144 hours.

Since ovum implantation occurs in rats of this colony around 120 to 135 hours after mating and since sperm were detected about 8 hours following mating, reduction in histamine concentration and content of gravid uteri took place just prior to implantation.

The author feels that these findings add evidence for a role of histamine in the mechanism of nidation related to induction of decidual cell reaction.

Stuart C. Silverberg

*Vol. 101, June, 1959.*

Kulangara, A. C., and Sellers, M. I.: Passage of Bacteriophages From Mother to Foetus in the Rat, p. 207.

*July, 1959.*

Maneesh, M. S., and Johnson, B. C.: Production of Dietary Vitamin K Deficiency in the Rat, p. 467.

**Public Health Reports**

*Vol. 73, November, 1958.*

\*Schachter, J., Waggoner, D. E., and Whelpton, P. K.: Short Range Birth Projections, p. 989.

**Schachter, Waggoner, and Whelpton: Short Range Birth Projections, p. 989.**

The authors present a refined method of estimating numbers of future births, based upon age and parity, for the period 1956-1965.

Two projections are made: "A," on the assumption that fertility trends would level off by 1960 and remain at that level until 1965, and, "B," that the fertility trends would be the same as in 1955 during the period 1956-1965. Thus, the authors present two projection estimates—Series A projects 4.45 million births in 1960 and 4.99 million in 1965, while the Series B projection estimates 4.26 million births and 4.76 million births, respectively, for 1960 and 1965.

Schuyler G. Kohl

*Vol. 74, April, 1959.*

\*Pasamanick, B., Dinitz, S., and Knobloch, H.: Geographic and Seasonal Variations in Births, p. 285.

**Pasamanick, Dinitz, and Knobloch: Geographic and Seasonal Variations in Births, p. 285.**

The authors have tabulated births in four selected groups of states by the month of births. These areas compared were: (a) Alabama, Louisiana, and Mississippi; (b) Minnesota and Wisconsin; (c) Maine, New Hampshire, and Vermont; (d) Washington and Oregon.

The authors were testing the hypothesis that the annual spring decline in births might be attributed to the discomforts of high summer temperatures and high humidity.

The findings were: (1) the southern states showed a marked decline in birth during the spring months and a corresponding peak in the number of late summer births; (2) the midwestern and northeastern states showed a lesser trough in spring births; (3) the northwestern states exhibited no spring trough at all; (4) male births are fewer just prior to and during the descending curve of the spring depression.

The following postulations are presented to explain the above findings: (1) uncomfortable temperatures reduce the frequency of coition; (2) there is an increased fetal death rate among conceptions occurring immediately prior to and during the summer months; (3) statistically, increased births during the summer automatically decrease the possibility of conception at this time and subsequent spring delivery.

The authors note that their unpublished data for Baltimore, Maryland, reveal that the trough



is greater for the low socioeconomic groups than for the higher economic groups who are capable of escaping the unpleasantness of the combination of high temperature and high humidity.

The essay is short and to the point and is illustrated with clear-cut and easily understood charts.

*Schuyler G. Kohl*

### **Zeitschrift für Geburtshilfe und Gynäkologie**

*Vol. 152, March, 1959.*

Thomas, J.: Investigation of Influence on Oxygen Saturation of Venous Blood by Malignant Tumors, Ionizing Rays and Pregnancy. Part I, p. 113.

Contamin, R.: Prepared Delivery, p. 145.

Slunsky, R.: On Damaging Effect and Histological Changes Following Infusion of Amniotic Fluid Into Rabbits, p. 162.

Prill, H. J.: Blood Supply of the Uterus. Part II, p. 180

\*Hodr, J., Herzmann, J., and Janda, J.: Changes of Some Components of Intermediate Carbohydrate Metabolism in the Course of Normal Labor, p. 202.

Ruck, C. J.: Crystal Test for Diagnosis of Rupture of Membranes, p. 215.

Lindaur, V.: On the Effect of Chlorpromazine on Spontaneous Activity of the Isolated Rat Uterus, p. 226.

**Hodr, Herzmann, and Janda: Changes of Some Components of Intermediate Carbohydrate Metabolism in the Course of Normal Labor, p. 202.**

Blood sugar, pyruvic acid, and inorganic phosphorus were studied in mothers and infants.

Maternal blood sugar averaged 80 mg. per cent at onset of labor. There was an average of 35 mg. per cent rise to the end of the first stage and another 50 mg. per cent rise to the end of the second stage. Pyruvic acid levels were found to rise from 1.7 mg. per cent to over 4 mg. per cent and 6.5 mg. per cent, respectively. No significant change was observed in inorganic phosphorus (3.2 mg. per cent, 2.7 mg., and 2.9 mg. per cent, respectively). Umbilical artery sugar level at birth after labors of about 7 hours is less than 65 mg. per cent. Then umbilical vein values are about 75 mg. per cent. Following labors of 11 to 18 hours, the umbilical artery carries 80 to 90 mg. per cent of sugar; the vein shows comparable changes.

Pyruvic acid level in the umbilical artery

after labors of less than 7 hours is 2.4 mg. per cent, in the umbilical vein 2.2 mg. per cent. In labors of 11 to 18 hours, the findings are almost 100 per cent higher. Inorganic phosphorus falls in the longer labors from 5.8 mg. per cent to 4.4 mg. per cent (artery) and from 5.0 mg. per cent to 4.6 mg. per cent (vein), respectively. The phosphorus change is not statistically significant.

*Walter F. Tauber*

### **Zentralblatt für Gynäkologie**

*Vol. 81, Feb. 28, 1959.*

\*Nakajima, T.: Ascorbic Acid Level and Ovulation, p. 337.

Gyory, G., Obal, F., and Szenasy, J.: The Value of Electroencephalograms in Following Infants Delivered by Cesarean Section, Forceps or Breech Extraction, p. 344.

Diegritz, H.: Partial Colpocleisis in the Absence of the Uterus, p. 351.

Schlipp, H.: Results of BCG-Inoculation 1953 to 1958, p. 354.

Zsolnai, B.: Clotting Disturbances in Pregnancy, p. 356.

**Nakajima: Ascorbic Acid Level and Ovulation, p. 337.**

Vitamin C levels were determined in 7 patients receiving gonadotrophic hormone, in 2 cycles of a healthy woman and in a man.

Basal temperatures, eosinophil counts, and vaginal smears gave parallel results. In 5 patients who responded to treatment and in the 2 cycles of the normal patient, the ascorbic acid level dropped at the time of ovulation. In the 2 patients who did not respond and in the male, there was no significant variation. Ovulation cannot be easily determined by ascorbic acid level alone. Apparently, the ovaries, adrenals, and pituitary regulate vitamin C levels.

*Walter F. Tauber*

*March 21, 1959.*

Bartsch, F.: Three cases of Cavemous Hemangioma of the Vagina in Pregnancy, p. 453.

\*Schrumpf, H.: X-ray Diagnosis of Postmaturity, p. 458.

Nölke, E. L.: Strength of Fetal Membranes and Their Rupture, p. 472.

Steglich, H.: Hemorrhage From an Umbilical Cord Hematoma in Labor—A Case Report, p. 480.

Rosenberg, H.: Controlled Hypothermia in the Treatment of Status Eclampticus—A Case Report, p. 481.



Röpke, F.: Is Prophylaxis for Ophthalmia Neonatorum Outdated? p. 485.

**Schrimpf: X-ray Diagnosis of Postmaturity, p. 458.**

In 50 suspected cases of postmaturity, x-rays were taken of the fetus in utero. Postmaturity was diagnosed with certainty if the distal femoral epiphysis was 10 mm. or over or if the proximal tibial epiphysis was 7 mm. or over; 17 babies fell into this category. There were 5 cases of "probable postmaturity" (femoral epiphysis 7 mm., tibial epiphysis 5 mm.), 7 of maturity (only femoral epiphysis present), and 7 were "barely mature" by size and absence of epiphyses. One definitely postmature baby died in utero without other apparent reason. One "barely mature" infant lived 7 hours (intracranial hemorrhage after spontaneous delivery). Runge's criteria of postmaturity were present at birth in 12 babies in whom definite postmaturity was also diagnosed radiologically, but in only 3 of the others. In view of the small, but definite, hazard to the fetus due to postmaturity, the author feels induction of labor is indicated for this diagnosis, but cesarean section is not.

*Walter F. Tauber*

*March 28, 1959.*

\*Preisler, O., Sigmond, I., and Stegmann, H.: Blood Type and Rh Factor in Carcinoma in Women, p. 493.

\*Buchholz, H. F.: Contribution on Extended Use of Vaginal Cytology With a Dry Fixation Technique, p. 498.

Schneider, G., and Muller, A.: Contribution on the Pathology of Placental Polyp, p. 501.

**Preisler, Sigmond, and Stegmann: Blood Type and Rh Factor in Carcinoma in Women, p. 493.**

The blood types and Rh factors of 1,076 women with carcinoma of pelvic organs and 100 women with carcinoma of the breast were compared to 4,017 controls (blood donors). Blood type A and presence of the Rh factor were more frequent in the cancer group to a statistically significant degree. Blood type A was also more frequent among 268 patients with carcinoma of the stomach than among the controls, but these patients did not differ from the general population in the occurrence of the Rh factor.

*Walter F. Tauber*

**Buchholz: Contribution on Extended Use of Vaginal Cytology With a Dry Fixation Technique, p. 498.**

A modification of the Papanicolaou method for the preparation of vaginal smears is described. After fixing the smear in a 90 per cent acetone, 10 per cent distilled water mixture for 10 to 30 minutes, the slides can be transported dry. The staining technique does not vary significantly from that of Papanicolaou. The quality of the slides is comparable. The advantages of the modification lie in easier transportation and reduced cost.

*Walter F. Tauber*

## Correspondence

### Common usage

*To the Editors:*

With reference to the article, "Common Usage," in the "Pertinent Comments" section of the October, 1959, issue of the JOURNAL, the term "functional uterine bleeding" has become an accepted term in recent literature very largely because of inconsiderate adoption and use by a number of medical writers. So far as etymology and use is concerned, the adjective "functional bleeding" should be used only to describe normal and cyclic menstruation. It describes perfectly and adequately the normal, cyclic phenomenon as it occurs in the human being, and it would seem proper to use it for this connotation. The fact the term was originally improperly used to describe what we now refer to as dysfunctional uterine bleeding is no justification for its continued use.

In a recent article in a standard textbook, functional uterine bleeding is described as the "abnormality which we think of as functional uterine bleeding." This definition is modified by the statement, "as some writers prefer to call it dysfunctional uterine bleeding." It would seem that most teachers and physicians in the field of gynecology and endocrinology should try to discard the term "functional" when referring to abnormalities of the process of menstruation and uterine bleeding.

From an etymological standpoint the term "dysfunctional uterine bleeding" seems to describe perfectly the abnormal processes of uterine bleeding which we are describing in a general way. The prefix "dys" is used generally to refer to disorders of a normal mechanism. It is a generally used prefix and a very well-understood one. The accepted definition of dysfunction as applied to medicine is "partial disturbances or impairment or abnormality of the functioning of an organ." According to Dorland's Dictionary, 23rd edition, the term "dysfunctional uterine bleeding" would be synonymous with the term "abnormal menstrual bleeding" or "abnormal uterine bleeding." There are times when the cause for it can

be very easily determined by relatively simple examinations. There are many times when the cause for it cannot be determined until extensive investigations have been utilized. The term is accepted as an admitting diagnosis for patients entering the hospital and can be modified by various adjectives which are more explanatory.

This is a plea to use the phrase "dysfunctional uterine bleeding," which is perfectly descriptive, in place of the phrase "functional uterine bleeding," which is not descriptive and has almost no connotation in the sense that it is being used.

Roy W. Mohler, M.D.

1806 Spruce St.  
Philadelphia 3, Pennsylvania

### Calculation of pregnancy rate

*To the Editors:*

A pregnancy rate of 5.7 per 100 years of exposure among clinic patients using a new contraceptive cream-jel (Immolin) without a diaphragm was reported by Drs. Finkelstein and Goldberg in the September issue of the JOURNAL. If this rate were correctly computed, it would place this method among the most highly effective contraceptive procedures now available.

Unfortunately, the reported pregnancy rate is not correctly computed. It is based on the experience of 176 women who used the prescribed method for 12 months or more out of a total of 366 women for whom the method was originally prescribed. The aggregate exposure of these 176 patients was 3,354 months. During this period 16 unplanned pregnancies occurred.

For each patient, "months of exposure" was determined by the number of months between the date of prescription and the date of conception, discontinuation of use, or the termination of the study. However, since the 190 women who became pregnant or dropped out of the study prior to the twelfth month were excluded from

the computation, effective observation of the remaining group began with the twelfth month rather than with the date of prescription. It is necessary, therefore, to deduct 11 months for each of the 176 patients (1,936 months in all) from the reported total of 3,354 months of exposure. This correction reduces the aggregate exposure to 1,418 months and increases the pregnancy rate to 13.5 per 100 years of exposure.

Although the above procedure is correct arithmetically, the resulting pregnancy rate is not comparable to rates published by other authors which, in general, include all months of exposure with use of a prescribed contraceptive method. Drs. Finkelstein and Goldberg kindly provided me with a complete tabulation by months of use and pregnancy status of all 366 patients who accepted the cream-jel. According to the table, the total exposure of the 366 patients amounted to 4,381 months during which 87 unplanned pregnancies occurred. Computed on this basis, the pregnancy rate is 23.8 per 100 years of exposure, a rate typical of those found among clinic patients using a jelly or cream without diaphragm.

Aggregate exposure of all 366 patients during the first year of observation totaled 2,963 months with 71 pregnancies, corresponding to a pregnancy rate of 28.8 per 100 years of exposure. The higher level of this rate, compared with the period from the twelfth month onward (13.5 per 100 years of exposure), reflects the greater risk of conception in the earlier period during which the least skillful and least interested couples tend to fall by the wayside. Owing to the greater risk of pregnancy in the early months of use, limitation of the study to patients who remain under observation for 12 months or more results in a spuriously low pregnancy rate, even when the first 11 months of exposure are correctly deducted.

The authors cite a recommendation by the Council on Pharmacy and Chemistry to the effect that "each case reported should be observed for at least 12 months." Since this formula assures a minimum of 11 pregnancy-free months in each case, it is statistically unsound and should never be used in the computation of pregnancy rates.

A joint subcommittee of the Margaret Sanger Research Bureau and the Planned Parenthood Federation of America is now working on a new set of criteria for the approval of chemical contraceptives. One of the recommendations agreed upon by this subcommittee stipulates that "the average period of observation during which the

material was used should be at least one year." Replacement of the Council's recommendation by the proposed new formula will help to avoid misleading results, such as those presented in the report by Drs. Finkelstein and Goldberg.

*Christopher Tietze, M.D.  
Director of Research  
National Committee on  
Maternal Health, Inc.*

*2 East 103 Street  
New York 29, New York  
Sept. 28, 1959*

### Arborizations in cervical smears

*To the Editors:*

The article by Drs. Schwalenberg and Efstation appearing on page 860 of the October issue of the JOURNAL includes a sweeping statement which, to a reader not fully informed of all the data on the subject of the mucus fern phenomenon, might be misleading.

The authors, referring to Ullery and Shabanah,<sup>1</sup> state, "they did not believe that arborization in the cervical mucus was an indication of progesterone deficiency."

It has always been argued by many obstetricians who took interest in the subject that some of their pregnant patients showed arborizations in their cervical smears at various stages of pregnancy and yet they were delivered normally at term.

We were the first to draw attention to the significance of this type of arborization as that depicted in the authors' Fig. 1, A—the atypical fern pattern.<sup>1-3</sup> This pattern occurs in about 30 per cent of nonpregnant women in the progestational phase and in some pregnant women who are apparently normal. We were, and still are, of opinion that this is the pattern to be seen in cervical smears when there is a dual activity by both estrogens and progesterone reflected in the smear. The poorer the pattern of arborizations the more dominant will progesterone be, and the opposite also holds true. Based on these observations and other clinical data, we concluded (paragraph 3, page 239) that "the presence of a fern reaction in the cervical smear during pregnancy does not necessarily mean placental insufficiency."<sup>1</sup> A cervical mucus smear which exhibits plentiful mucoid material and abundant exfoliation denotes apparent progestational domi-

nance. Some of these smears will show, in addition, this pattern of poor arborization or atypical ferning. When this is the case, the patient is in no danger of progesterone deficiency. But when the proportion of ferning increases and *continues to do so*, placental insufficiency becoming irreversible, the mucoid material and exfoliation inevitably diminish, and the picture becomes that of clear heavy ferns, as depicted in Fig. 7 of our article (page 238).<sup>1</sup>

The authors' statement (paragraph 1, page 862) that "All patients *who repeatedly showed heavy arborizations* of the cervical mucus were treated with progesterone," etc., speaks for itself as simply a confirmation of our findings and is basically similar to our statement. In the authors' series of 200 patients, 6.5 per cent had abortions, a similar finding to our 6.6 per cent.<sup>1</sup>

The fact that the other patients who did not have abortions showed unusual symptoms which vanished with reversal of the cervical mucus findings is not a unique experience. If the authors would revise the smears taken from these patients, using the index-of-refraction liquids—a test for the detection of electrolyte imbalance adopted to clinical usage by myself<sup>4</sup>—they will find that there was an imbalance between sodium and potassium chloride, the latter being in excess of the normal. A good, reliable nontoxic diuretic would have relieved these patients of their symptoms without changing the ferning reaction quantitatively but only qualitatively. It is less expensive and more convenient and is easy to handle.

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E. H. Shabanah, M.D.

1002 Central Ave.  
Saskatoon, Saskatchewan  
Oct. 15, 1959

#### Reply by Drs. Schwalenberg and Efstation To the Editors:

Dr. Shabanah states in his original article<sup>1</sup> in a study of 95 cases: (A) "Thirty per cent of

all pregnant patients show arborization in varying amounts in all stages of pregnancy"; (B) "The presence of arborization does not necessarily mean placental insufficiency." We believe these statements are misleading.

We recognize the difference between "typical" and "atypical" arborization. Our studies<sup>2</sup> have indicated that the positive smear may, at certain areas of pregnancy, be so common as to be considered normal, but is not more common than 11.6 per cent. This we found to be true in 200 patients with over 2,000 carefully studied and annotated slides, and is now true of more than 500 patients with over 5,000 smears. Our incidence of positive smears agrees more closely with Zondek's series<sup>3</sup> of 226 cases with an incidence of 12 per cent arborization in pregnancy.

We will happily retract the statement that Dr. Shabanah does not believe arborization of pregnant cervical mucus is an indication of progesterone deficiency, particularly so if this will impress upon the minds of the readers that such a condition may exist.

The aforementioned article<sup>2</sup> was offered to emphasize the importance of cervical mucus studies in pregnancy to the average obstetrician. No one can at present determine which patient will continue to show arborization and which will progress to an irreversible deficiency. For these reasons we emphasize, with Dr. Shabanah, that a repeatedly positive cervical mucus must be reverted by treatment with progesterone to a negative smear.

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3. Zondek, B., Forman, I., and Cooper, K. L.: *Fertil. & Steril.* 6: 523, 1955.

R. R. Schwalenberg, M.D.  
T. D. Efstation, M.D.

Tiffin, Ohio  
November, 1959

#### Index-of-refraction liquids

To the Editors:

The article entitled "The Nasal Mucus Smear in Toxemias of Pregnancy," which appeared in the December, 1958, issue of the *JOURNAL* (page 1248), describes a simple procedure for the detection of electrolyte imbalance.



The index-of-refraction liquids constitute the basis for this test, and many readers have made personal inquiries as to the source of these liquids.

It might, therefore, be helpful to all who wish to pursue this work to be informed that these liquids are obtained from Cargille Scientific, Inc., 117 Liberty Street, New York 6, New York.

*E. H. Shabanah, M.D.*

1002 Central Ave.  
Saskatoon, Saskatchewan  
Oct. 13, 1959

### Successful antioinsemination

*To the Editors:*

On page 274 of the August, 1959, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYN-ECOLOGY, there is an article titled "Sterility Due to Retrograde Ejaculation of Semen," by Donald Walters and Morton S. Kaufman. The authors state that theirs is the second case report of a successful autoinsemination.

They were apparently unaware of the article, "Artificial Insemination With Semen Recovered From the Bladder," by Robert S. Hotchkiss, Asdrubal Baias Pinto, and Sophia Kleegman, which appeared on page 37 of the January-February, 1955, issue of *Fertility and Sterility*. In this article it was reported that three cases of known conception were achieved by utilizing spermatozoa recovered from the bladder. Fischer and Coats reported two such cases, making a total of five in all prior to this recent case.

In summary, there have been at least three

case reports on this subject including the one by Walters and Kaufman, and there have been at least six known cases of conception utilizing spermatozoa from the bladder.

*Bernard A. G. Weisl*

450 West 24th St.  
New York 11, New York  
Aug. 26, 1959

### Reply by Drs. Walters and Kaufman

*To the Editors:*

Dr. Bernard A. Weisl is essentially correct in his letter of Aug. 26, 1959. We had not found the article, "Artificial Insemination With Semen Recovered From the Bladder," by Robert S. Hotchkiss, Asdrubal Baias Pinto, and Sophia Kleegman, in which sperm from the bladder was utilized and in which the patient was delivered of a full-term infant twice. A second patient was pregnant at the time the article was written.

We did make reference to the article by Irving C. Fischer and Edward C. Coats (Obst. & Gynec. 4: 352, 1954). They reported a full-term pregnancy and a miscarriage in the same patient when sperm from the bladder was utilized.

We are very appreciative of the fact that Dr. Weisl brought these additional cases to our attention.

Our case is the sixth such insemination reported in the literature.

*Donald Walters, M.D.  
Morton S. Kaufman, M.D.*

1835 Eye St., N.W.  
Washington 6, D. C.  
Oct. 30, 1959

## Items

### **American Board of Obstetrics and Gynecology**

The next scheduled examinations (Part II), oral and clinical, for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 11 through 16, 1960. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I Examinations will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of new and reopened applications for the 1961 examinations is Aug. 1, 1960. Candidates are urged to submit their applications as soon as possible before that time.

*Robert L. Faulkner, M.D.  
2105 Adelbert Road  
Cleveland 6, Ohio*

### **Central Association of Obstetricians and Gynecologists meeting**

The annual meeting of the Central Association of Obstetricians and Gynecologists will be held in Kansas City, Missouri, Oct. 6 to 8, 1960.

A scientific program will be presented on each of the mornings of October 6, 7 and 8. On Friday afternoon, October 7, a special scientific program will be presented by the Kansas City Gynecological Society. Physicians who are not members of the Association, as well as interns and residents, are invited to attend.

### **Central Association of Obstetricians and Gynecologists award**

The Central Association of Obstetricians and Gynecologists offers an annual award of \$250.00 for outstanding investigative or clinical work in the field of obstetrics and/or gynecology. Any accredited physician, research worker, or medical student living within the geographic confines of the Central Association is eligible. Papers must be written expressly for this competition and they must be original. It is customary that the winning paper be presented at the annual meeting, the next of which will be held in Kansas City, Missouri, Oct. 6 to 8, 1960.

Manuscripts should be submitted to the Secretary in triplicate, accompanied by an abstract not to exceed 150 words. No author's identification shall be shown on any of the three copies, the only identification being a covering letter addressed to the Secretary.

Manuscripts should be in the hands of the Secretary by not later than July 6, 1960.

*Herman L. Gardner, M.D., Secretary  
633 Hermann Professional Building  
Houston 25, Texas*

### **The Carl G. Hartman grant-in-aid**

Applications for the Carl G. Hartman grant-in-aid in the amount of \$500.00 should be sent to the Secretary of the Awards Committee of the American Society for the Study of Sterility, Dr. Robert B. Wilson, 200 First Street, Southwest, Rochester, Minnesota, by Feb. 29, 1960. Applications must be accompanied by five copies of a brief outline of the proposed research project.



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1. Kistner, R. W.: Conservative Treatment of Endometriosis, *Postgrad. Med.* 24:505 (Nov.) 1958. 2. Southam, A. L.: Symposium on Enovid: Clinical Application of Enovid and Other Progestational Agents in Control of Menstrual Disorders, Chicago, Searle Research Laboratories, 1959, pp. 11-14. 3. Roland, M.: Effects of Norethynodrel on the Human Endometrium, *Ann. New York Acad. Sc.* 71:638 (July 30) 1958. 4. Kupperman, H. S., and Epstein, J. A.: A Symposium on 19-Nor Progestational Steroids: Gonadotropic-Inhibiting and Uterotropic Effects of Enovid, Chicago, Searle Research Laboratories, 1957, pp. 32-45. 5. Weinberg, C. H.: Symposium on Enovid: Enovid for Relief of Dysmenorrhea and Control of Dysfunctional Bleeding and Endometriosis, Chicago, Searle Research Laboratories, 1959, pp. 19-24. 6. Greenblatt, R. B.: Symposium on Enovid: Progesterone and Progestins: Their Limitations and Comparative Values, Chicago, Searle Research Laboratories, 1959, pp. 4-10.

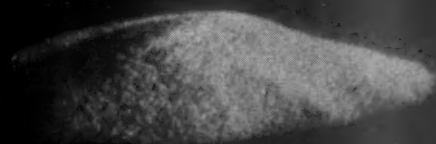
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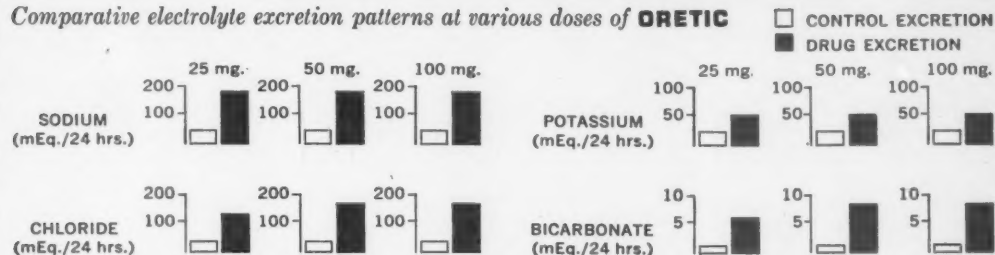




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**Bibliographical Note:** The investigators quoted have published their findings in the September, 1959 issue of *Current Therapeutic Research*. The study, entitled **CLINICAL PHARMACOLOGIC OBSERVATIONS ON ORETIC, A NEW ORALLY ACTIVE DIURETIC AGENT**, can be found in that publication on pages 26 through 33.



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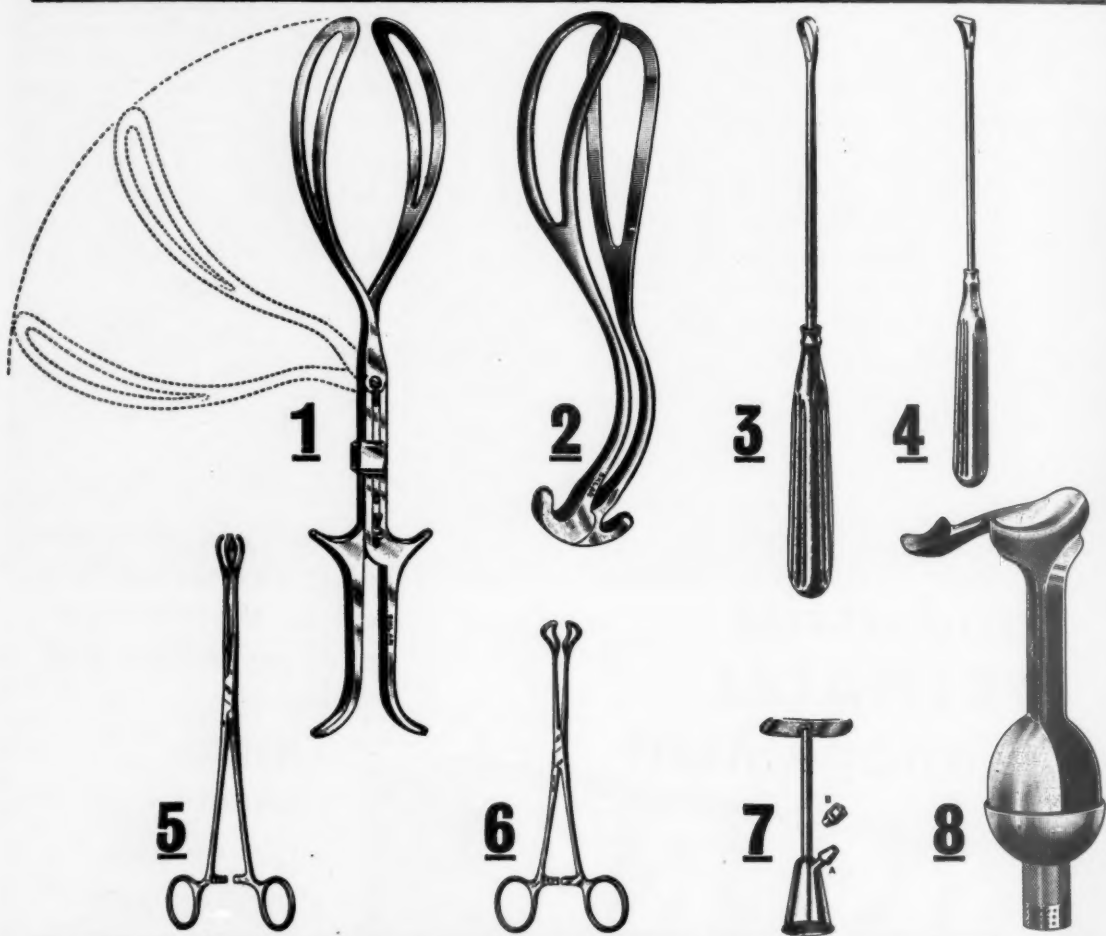
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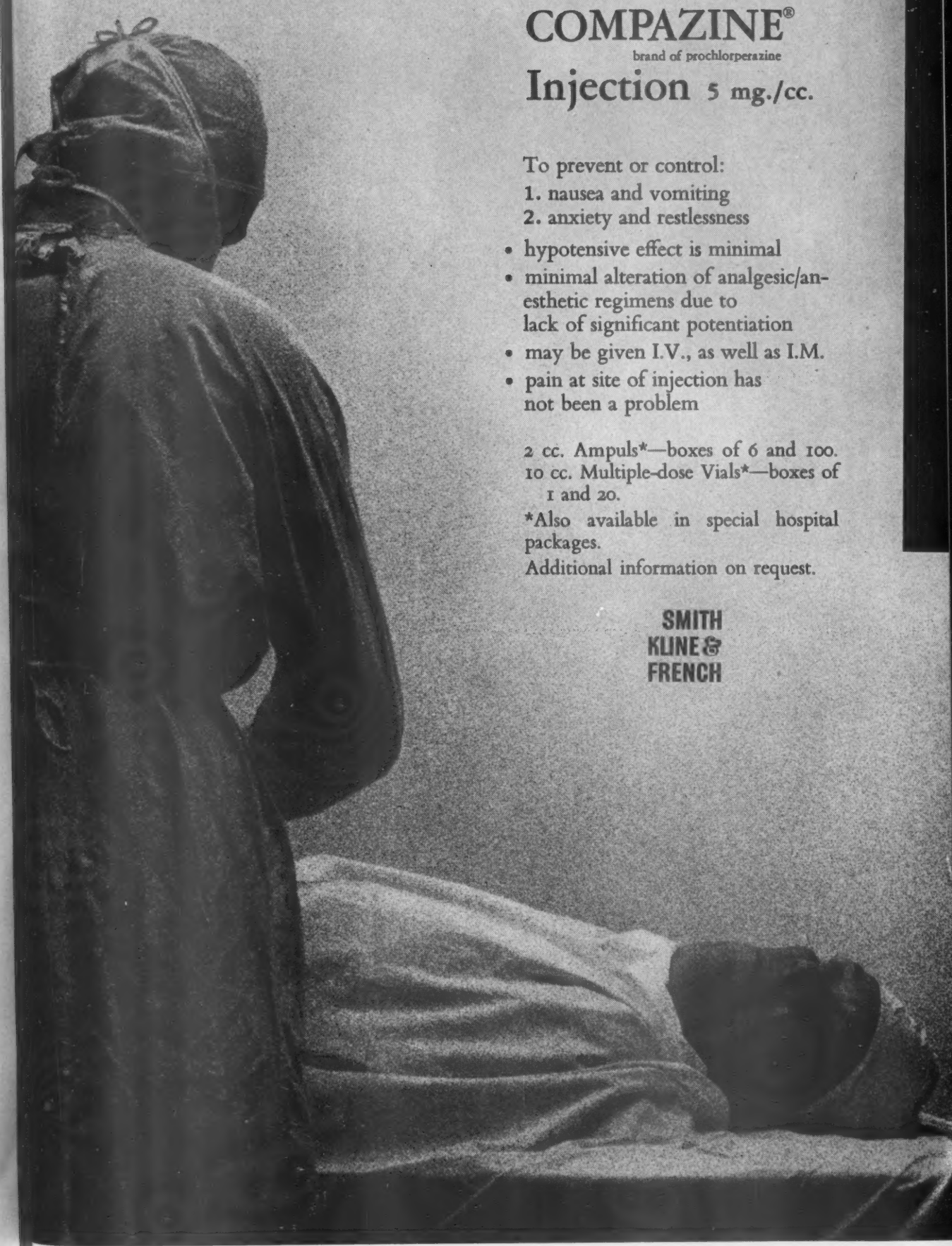
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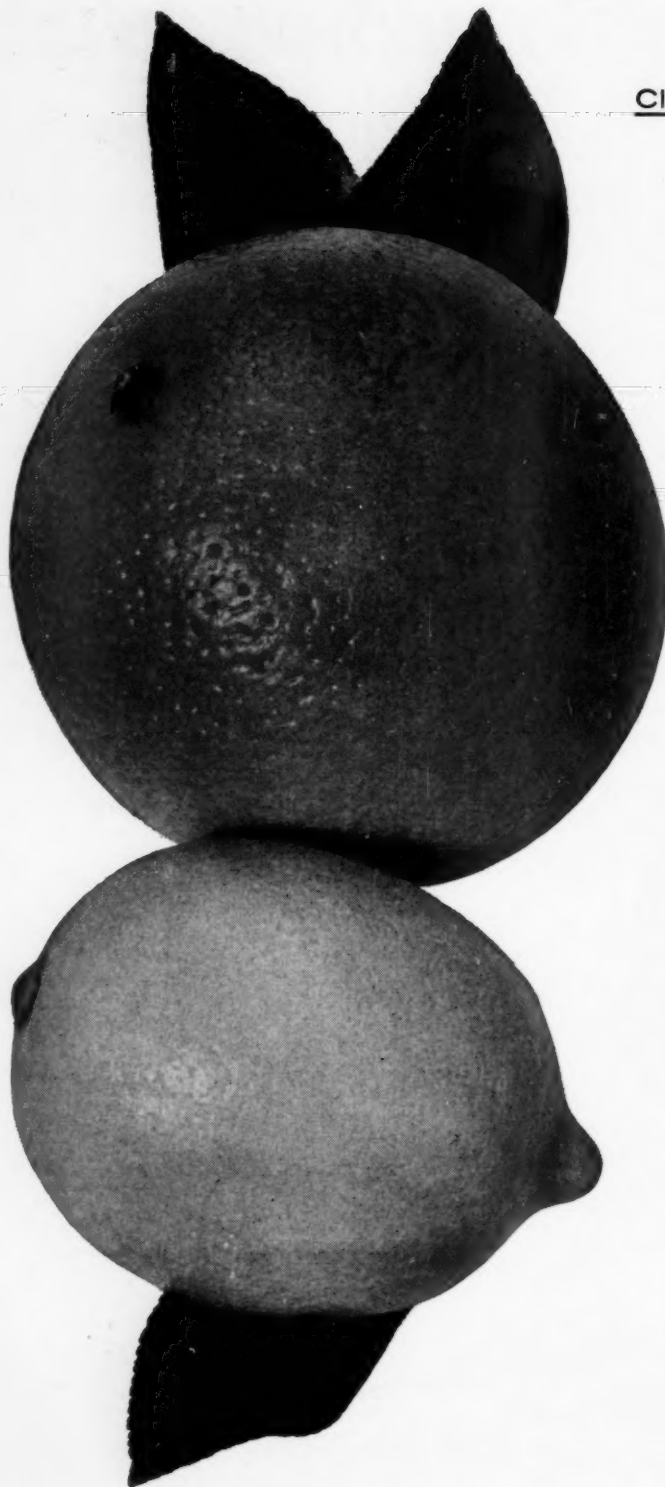
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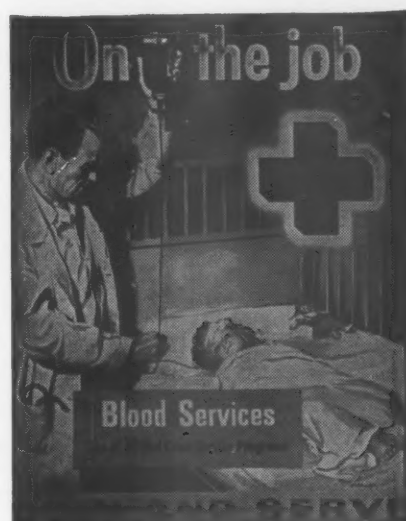
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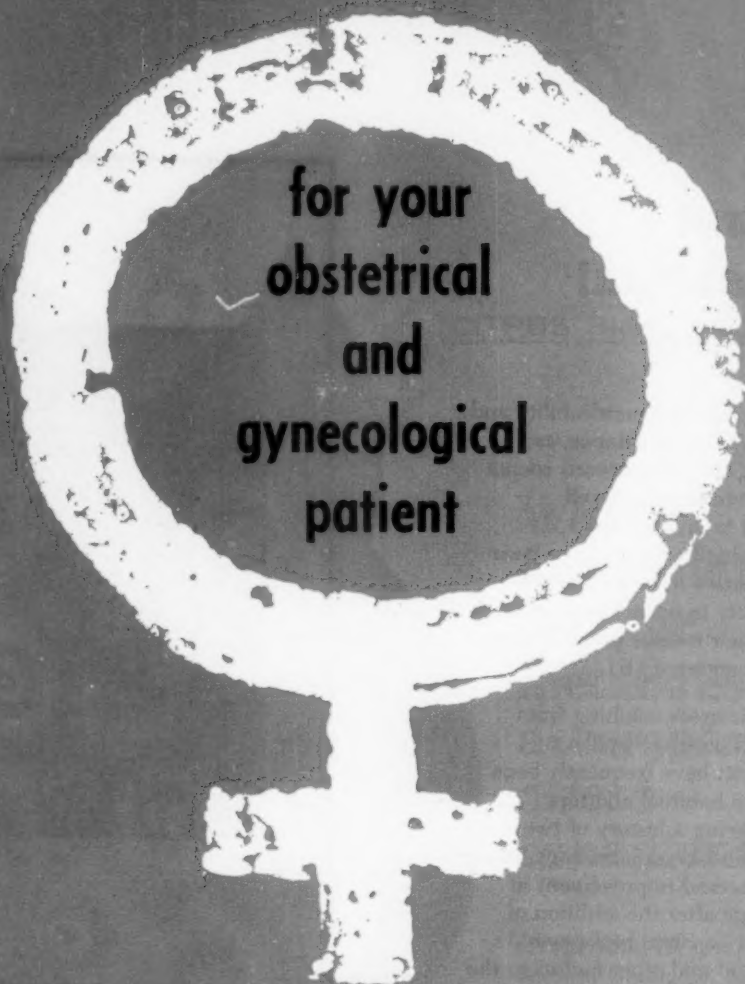
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*Reference: 1. Peña, E. F., Med. Times, 82-921, 1954.*



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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint.  
Current M. Digest  
25:68, Feb. 1958.

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*Mornidine—brand of pipamazine*

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Clinicians report that 91 per cent of 145 pregnant patients treated for nausea and vomiting with Mornidine had "excellent" or "good" relief of symptoms. Mornidine was found to have a distinct advantage in that the drug was an effective antiemetic<sup>1</sup> in smaller doses than those required when other currently available phenothiazines were employed. Side effects were minimal.

Excellent results were obtained with Enovid by Rakoff<sup>2</sup> in thirty-eight patients with threatened and habitual abortion; only twelve aborting. No evidence of androgenicity was observed. Not a single patient complained of nausea, and therapy did not have to be discontinued because of any side effects. Chalmers<sup>3</sup> used Enovid in dysfunctional uterine bleeding. It "appears to be the most effective progestational agent which I have used. . . ."

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Maeder<sup>5</sup> mentions Floraquin as an effective product to use.

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### References:

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9. Council on Drugs: *New and Nonofficial Drugs 1959*, Philadelphia, J. B. Lippincott Company, 1959, p. 520.



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the endometrium, hence  
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*to stop as well as prevent  
nausea and vomiting of pregnancy*

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completely  
different  
antiemetic  
antinauseant

*available in oral, parenteral  
and suppository forms.*



*for a pregnancy unmarred by "morning sickness,"  
uncomplicated by hyperemesis gravidarum*

TIGAN is equal in effectiveness to the most potent antiemetics. It not only safely prevents "morning sickness," but usually stops even severe, intractable vomiting.<sup>1</sup>

#### Acts at the CTZ—like the most potent antiemetics

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),<sup>2</sup> a medullary structure which activates the vomiting center. To this extent, Tigan is like the most potent antiemetic agents—the phenothiazines.<sup>3</sup>

#### Safe—without the side effects of the antihistamines

In extensive clinical studies,<sup>1,4-6</sup> Tigan has demonstrated a virtually complete absence of side effects. It has no sedative properties;<sup>4-6</sup> therefore, patients receiving Tigan may drive an automobile without the hazard of drowsiness, and carry on their household activities without being troubled by added lethargy or sleepiness.

#### Safe—without the risks of the phenothiazines

The mode of antiemetic action is the only similarity between Tigan and the phenothiazines. Chemically and pharmacologically, they are completely unrelated.<sup>2</sup> Tigan has no tranquilizing properties, hypotensive action, supramedullary effects, extrapyramidal tract stimulation or hepatic toxicity.<sup>1,4-6</sup> In laboratory findings there has been *not one reported instance of abnormality due to Tigan*.<sup>1,4-6</sup>

#### No known contraindications

There are no known contraindications, no special precautions to complicate Tigan therapy.

# Tigan

*no known contraindications...no sedative properties...no tranquilizer side effects*

**Dosage:** Usual recommended adult dose of Tigan is 200 mg initially, to be followed by doses of 100-200 mg q.i.d. as required. In nausea and vomiting of pregnancy satisfactory control is usually achieved by an initial dose of two capsules (200 mg) immediately upon awakening. For the patient whose nausea and vomiting is not confined to the morning hours, supplemental doses of 100 mg should be given throughout the day at intervals of three to four hours.

**Available:** Capsules, 100 mg, blue and white; bottles of 100 and 500. Ampuls, 2 cc (100 mg/cc); boxes of 6 and 25. Pediatric Suppositories, 200 mg; boxes of 6.

#### References:

1. Reports on file, Roche Laboratories.
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*Literature and samples on request*

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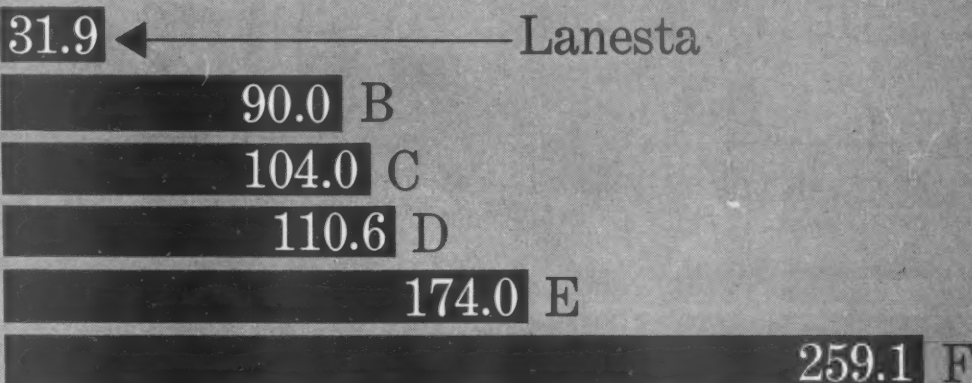


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*References:* 1. Berberian, D. A., and Slichter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958. 2. Bailey, J. H.; Coulston, F., and Berberian, D. A.: J. Am. Pharm. A. (Sc. Ed.) 48:212 (April) 1959. 3. Gamble, C. J.: Am. Pract. & Digest Treat. 9:1818 (Nov.) 1958. 4. Berberian, D. A.; Coulston, F., and Slichter, R. G.: Toxicol. & Appl. Pharmacol. 1:366 (July) 1959. 5. Warner, M. P.: J. Am. M. Women's A. 14:412 (May) 1959.

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5



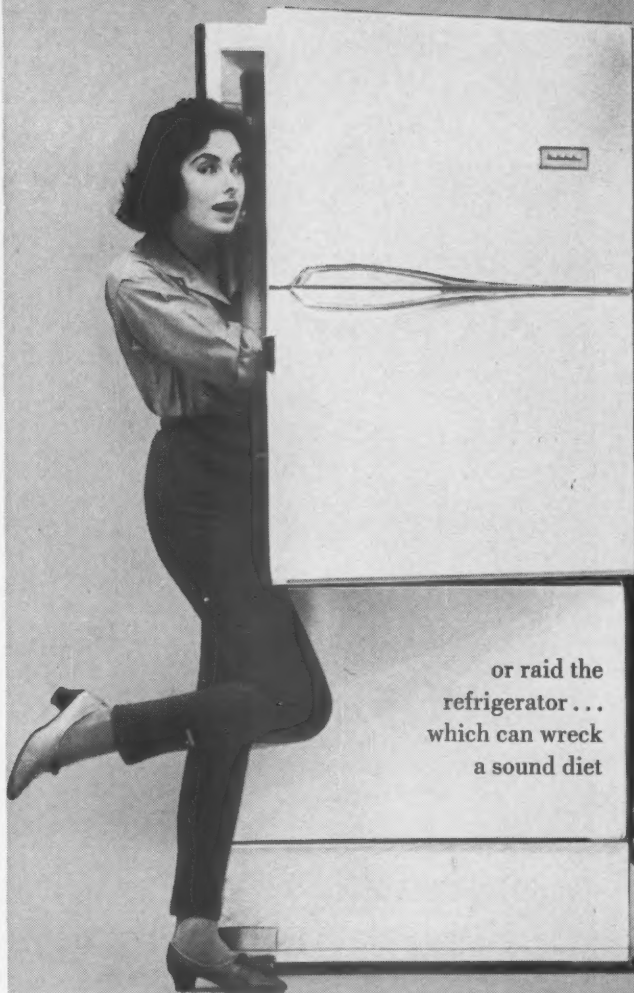
Before meals  
or at bedtime . . .





or skip meals,  
now and again

3



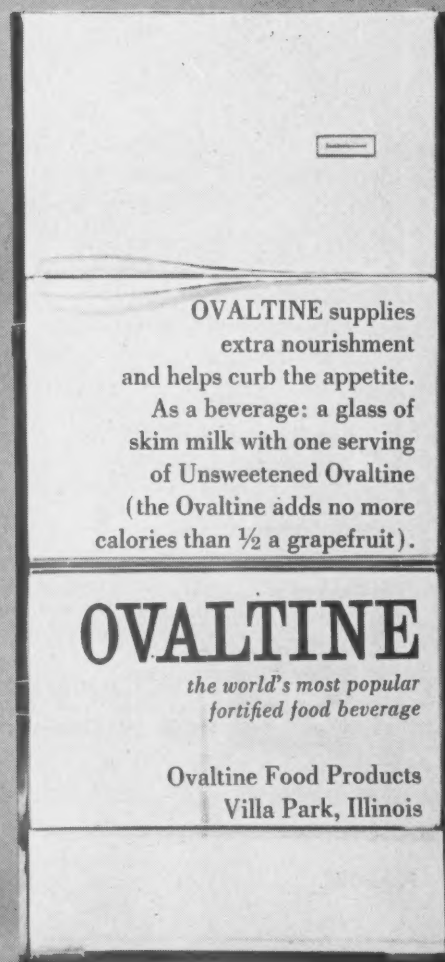
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1. Moessner, G.F.: To be Published, Western J. Surg.

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\*Agriculture Handbook No. 62, U. S. Department of Agriculture, 1957 (Sept.) p. 33.

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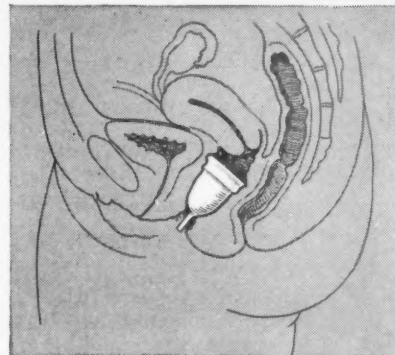
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*references:* (1) Voulgaris, D. M.: Dysmenorrhea—Treatment with Isoxsuprine, *Obstetrics and Gynecology*, to be published. (2) Busky, A. H., to be published.

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\*Traylor, J. B., and Torpin, R.: *Am. J. Obst. & Gynec.* 61:71-74 (Jan.) 1951.

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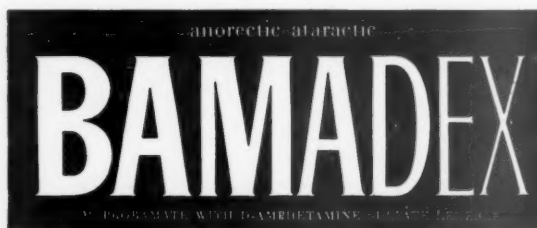
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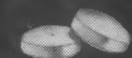
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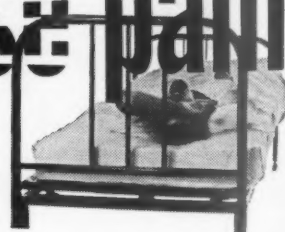
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